Intravenous Immune Globulin Market in the United States

Year	Dollars (MM)	Change Percent	Units (000)*	Change Percent
1986	49.9	+ 66	550	+ 68
1987	83.5	+ 67	930	+ 69
1988	122.9	+ 47	1,510	+ 62
1989	171.3	+ 39	2,204	+ 46
1990	190.1	+ 11	2,659	+ 21
1991	207.9	+ 9	3,073	+ 16
1992	235.5	+ 13	3,731	+ 21
1993	296.6	+ 26	4,987	+ 34
1994	349.3	+ 18	5,484	+ 9
1995	385.3	+ 10	6,050	+10
1996	427.5	+ 11	6,620	+ 9
1997	437.7	+ 3	6,560	- 2
1998	559.0	+ 28	6,220	- 5
1999	755.0	+ 35	6,680	+ 7
2000	837.3	+ 11	7,012	+ 5
2001	1,041.9	+ 24	8,685	+24

* 2.5 gram equiv.

4.2.2) RESULTS BY COMPANY

In 2001, Baxter was the market leader with 23.3% of total sales, followed by the American Red Cross with 22.7%. Bayer was in third position with 18.3% market share, and Aventis Behring had 14.9%.

Alpha Therapeutic

In 2001, Alpha Therapeutic's IGIV sales revenues amounted to $76.5 million. This company was virtually shut down by the FDA for most of 2000 and resumed full production in August 2001. From that time on, it increased its market share on the IVIG market, using a low pricing policy.

Venoglobulin-I was introduced in the United States in 1989 and Venoglobulin S in 1996. The 10% "Venoglobulin S" formulation was approved by the FDA in early 1995. In 1997, Venoglobulin S received approval for the treatment of Kawasaki Disease. In 1998 the 10% solution was approved for its storage at room temperature.

American Red Cross

In 1998, the American Red Cross (ARC) introduced "Panglobulin", a product identical to "Sandoglobulin". It is manufactured by ZLB Bioplasma (formerly Central Laboratory of the Swiss Red Cross) in Bern from ARC non-paid donor plasma. The sales of this product amounted to about $54.4 million in 2001 (+1.0% over 2000). The sales of "Polygam SD", the ARC's other IGIV, amounted to approximately $182.1 million (+66.7%).

When Novartis negotiated its contract with the ZLB in 1997, the exclusivity of Novartis for the distribution of the ZLB's IGIV was terminated for two countries, the United States and Switzerland. This enabled the ZLB to negotiate an agreement with the American Red Cross for the distribution of "Panglobulin" in the U.S. This product has the same profile as Sandoglobulin: it is manufactured by the same fractionator, and with the same plasma of American origin.

Aventis Behring

In 2001, Aventis Behring's sales of "Gammar P-IV" amounted to about $155.3 million, a 11.1% increase from 2000. Aventis Behring is reported to be developing a liquid version of "Gammar P-IV" although the product is not in clinical trial as yet.

Baxter Bioscience

In 2001, estimated sales revenues from Gammagard SD (and Iveegam, for a small share) amounted to $242.3 million, a 18.6% increase in dollars from 2000. Besides primary immune deficiency and ITP, Gammagard SD is approved for B-cell chronic lymphocyte leukemia (CLL), giving this product a competitive advantage over others. The

product has a lower IgA content than other preparations. Furthermore, Gammagard's CMV titer is higher than the other products, and this constitutes another advantage.

A 5% liquid formulation of Gammagard SD has been developed and is expected to be submitted to the FDA in the near future. A 10% solution is also in development.

Bayer

In 2001 the sales of Gamimune-N amounted to $190.4 million, a -3.7% decline from 2000 in dollars. Over 95% of Gamimune-N sales are generated by the 10% formulation introduced in 1992. Gamimune-N is approved for:

- Primary Humoral Immunodeficiency,
- Idiopathic Thrombocytopenic Purpura,
- Bone Marrow Transplantation, and
- Pediatric HIV infection.

In 1996, a virus inactivation step (solvent detergent) was added to the product. Bayer has developed new liquid IVIG preparation, using a novel technology. It will be manufactured in a dedicated facility in North Carolina. "Gamunex" may be introduced in 2003.

ZLB Bioplasma

In 2001, the sales of ZLB IVIG amounted to about $111.6 million. This was achieved as ZLB Bioplasma took over many of the accounts of Novartis.

Although ZLB IVIG was well accepted because it took over from Sandoglobulin, a well known product, it remains a second generation IVIG, priced at the lower end of the price range. Product enhancements, such as nanofiltration, liquid formulation, and 12% concentration are reported to be in development in Bern.

4.2.3) IVIG PRICING

IVIG prices in the United States

Product	Price per gram Through 2001	Q/1/2002
Gamimune-N	$54.0	$49.0
Venoglobulin S	$51.0	$46.0
Gammagard SD *	$49.7	$45.0
Gammar P-IV	$46.0	$42.0
Polygam SD	$47.0	$41.0
Panglobulin	$44.0	$40.0
Sandoglobulin	$42.0	N.A.
ZLB Bioplasma IGIV	$42.5	$40.0

In 2002, the price of IVIG began to decline, and by mid 2002, the price was lower by 10% to 15% than at the end of 2001.

Until 1987, IGIV prices were set at a relatively high level by both Bayer and Novartis, despite rebate programs and other "charge backs" which represented as much as 20% of the list price. In the early 1990's, several companies entered the IGIV market and began to offer their product at competitive prices, pulling the average selling prices down, except for Sandoglobulin which was consistently higher than the average. In 1995, however, Novartis modified its pricing strategy and Sandoglobulin was no longer the most expensive IGIV product, putting an end to its traditional image of a "high price" product. Instead, Gamimune-N and Venoglobulin S became the most expensive products. In 2001, the average price for all the products was estimated at $48 per gram, 80% higher than in 1997.

While the average price of IGIV declined from 1987 to 1994, the trend changed in 1995, as the price of IGIV began to climb, due to a combination of such factors as product scarcity, higher cost of plasma, PCR testing, virus inactivation processes, and possibly the necessity for some of the manufacturers to make up for lower revenues from plasma-derived Factor VIII and albumin.

Average Selling Prices of IGIV Per Gram
From 1986 to 2000

Year	Average Selling Price	Percent Change
1986	$36.29	-
1988	$32.56	- 9.3%
1990	$28.60	- 8.0%
1991	$27.06	- 5.4%
1992	$25.25	- 6.7%
1993	$23.79	- 5.8%
1994	$25.48	+ 7.0%
1995	$25.47	-
1996	$25.83	+ 1.4%
1997	$26.69	+ 3.5%
1998	$35.95	+34.7%
1999	$45.20	+25.8%
2000	$47.73	+ 5.6%
2001	$47.99	+ 0.5%

4.2.4) IGIV Distribution

It is estimated that 65% of the IGIV sold in the country is distributed to hospitals through their Group Purchase Organizations (GPOs). Home care companies comprise about 20% of the market, and the remaining 15% of the market includes sales to dealers and distributors. In 1998, the manufacturers shifted slightly their distribution in favor of the hospitals, as abuses in the spot price of IGIV (reportedly up to $120 per gram and more) were denounced by the media and in various government meetings. It is estimated that the share of the sales to distributors went down by some eight to ten percentage points, while the share to hospitals increased accordingly. Today, the situation has not changed significantly although distributors are seen as a convenient outlet for product which is either short-dated or in excess supply.

Outpatient hospital infusion offices, "infusion suites" and other similar outfits - under physician's supervision - are a growing market, although still relatively small.

Home infusion therapy using IGIV has become successful in recent years, as physicians and patients appreciated the convenience of the procedure, although some controversy still surrounds it. Home IGIV therapy is easier for the patient and possibly less expensive as it avoids long hospital stays, but it carries some liability risk.

The home care companies (Caremark, Gentiva, etc) buy IGIV directly from the manufacturers, usually at a price which is not competitive with the price paid by large hospital groups. This market segment is not growing as fast as such novel facilities as "ambulatory infusion centers" which are a bridge between the hospital and the home care company.

4.2.5) IGIV and Disease Conditions

After reviewing all published reports in the past twelve years, an expert panel sponsored by the University Hospital Consortium concluded in 1995 that there was little evidence to support most off-label clinical usage of IVIG. The panel comprising physicians and pharmacists noted that information on most off-label uses generally originated from anecdotal reports or from uncontrolled or inadequately controlled studies. "In those few situations in which effectiveness has been demonstrated, IVIG is indicated only if standard approaches have failed, if they become intolerable, or if they appear "contraindicated". Although the various products commercially available have obtained FDA approval for primary immunodeficiency, ITP, Kawasaki syndrome, bone marrow transplantation, chronic lymphocytic leukemia and childhood HIV infection, they have also been used for 53 specific off-label applications, mainly in hematology, immunology, neurology, rheumatology, gastroenterology and oncology. The panel also took exception to common characterizations of IVIG as an "innocuous" product, citing the known risks of aseptic meningitis, anaphylaxis and anaphylactic reaction.

This was the beginning of other initiatives to restrict the use of IGIV in off-label indications. Today, a number of hospitals have established guidelines on the appropriate use of IGIV, virtually banning its use in dubious medical indications.

Despite the recommendations to limit the use of IGIV in off-label indications, the product still appears to be a last resort therapy for many hard-to-treat conditions.

4.2.6) CURRENT RESEARCH DIRECTIONS

Although the shortage has drastically reduced the degree of clinical research with IGIV, it is reportedly tried in the disease conditions listed below.

- Diabetic Neuropathies
- Myasthenia Gravis
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Severe, steroid-dependent Asthma
- Multiple Sclerosis Bayer is reported to be conducting a trial for this indication which affects some 350,000 people.
- Spontaneous Abortions
- Guillain-Barré Syndrome (GBS) IGIV is being used experimentally to treat acute Guillain-Barré Syndrome (GBS), one of the most common causes of acute generalized paralysis, affecting between one and two people per 100,000 each year. The cause of Guillain-Barré syndrome is still unknown, making the evaluation of treatment difficult. Several clinical trials have led to the approval of IGIV in the treatment of GBS in Europe.
- Inhibitors to Factor VIII
- Parkinson Disease

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

FRACTION V (ALBUMIN + PPF)

COMPANY	UNITS * (000)	A.S.P. * $	DOLLARS (MM)	MARKET SHARE	KILOGRAMS	CHANGE FROM '00	
						UNITS	DOLLARS
Alpha Therapeutic	645	35.50	22.898	9.85%	8,063	330.0%	330.0%
Aventis Behring	1,300	33.00	42.900	18.46%	16,250	30.0%	17.5%
Baxter	1,750	34.20	59.850	25.76%	21,875	40.0%	31.2%
Bayer	375	33.50	12.563	5.41%	4,688	-16.7%	-23.5%
American Red Cross	2,050	35.10	71.955	30.97%	25,625	-11.6%	-17.3%
Massachusetts Lab.	10	34.00	0.340	0.15%	125	-44.4%	-46.8%
ZLB Bioplasma	705	31.00	21.855	9.41%	8,813	-3.4%	-14.5%
Total	6,835	34.00	232.360	100.0%	85,438	15.1%	6.7%

The recombinant factor concentrates have largely displaced the plasma-derived Factor VIII and IX products. The genetically engineered products are now used by the majority of hemophilia A and B patients,

6.2) Hemophilia Patient Population

The size of the hemophilia population has not changed significantly in recent years. Starting in 1997, the Centers for Disease Control began collecting demographic data primarily for the purpose of monitoring viral markers and the health status of hemophilia patients. A national surveillance program called "Universal Surveillance Collection" (UDC) collects data from the 140 federally-supported Hemophilia Treatment Centers (HTCs) across the nation where an estimated 70% of patients with bleeding disorders are cared for. According to the Centers for Disease Control, the following patients population was estimated in 1994 (latest data available):

Type of Bleeding Disorder	1994
Hemophilia A	13,320
Hemophilia B	3,640

The Centers for Disease Control (CDC) has not updated the above numbers. In 1996, the 8,321 patients recorded as "suffering from other bleeding disorders" included 5,321 individuals with von Willebrand's disease (vWD). In early 2000, the CDC reported 6,743 individuals suffering from vWD. The growth of this sub-population of patients (+7.5%) was not only attributed to population growth and lower AIDS mortality, but mainly to improved diagnosis and wider public awareness of the deficiency. In particular, the actions of the NHF and other organizations increased the public's awareness of vWD.

The number of patients with inhibitors is controversial, with percentage ranging from 5% to 30% for hemophilia A patients, and about 4% to 10% for hemophilia B. Several assumptions must be taken into account when considering these numbers: for example, whether the inhibitor is stable or transient, whether it is at a high or low level. It is generally agreed that the inhibitor appears among infants, and may

disappear within one to two years if treated by an immune tolerance regimen.

For the purpose of estimating the patient population, and based on surveys conducted in early 2000 and before, the number of hemophilia A or B patients with an inhibitor is approximately 1,500 (13,300 x 11% = 1,460) + (3,300 x 4% = 130) = 1,590 patients, rounded up to 1,600.

The hemophilia treatment centers maintain a roster of the patients who have been seen at least one time. The "active" patients are defined as those who visit a treatment center at least once a year for a medical check up. Therefore the number of "active" patients underestimates the actual number of hemophilia patients. Furthermore, some patients, in particular the mild ones, only have infrequent contacts with a treatment center, for example in emergencies. In 1995, the Centers of Disease Control reported as many as 4,541 "inactive" patients, most of whom were "lost to follow up".

The percentage of severe, moderate and mild patients recorded among Hemophilia A and Hemophilia B in six states is estimated as follows:

Degree of Severity	Hemophilia A	Hemophilia B
Severe	42.3%	33.8%
Moderate	23.2%	32.1%
Mild	32.0%	30.8%
Unknown	2.5%	3.3%
Total	100.0%	100.0%

Every year, about 400 couples are at risk of having a child with hemophilia. In addition, about 100 children are born with a clotting disorder due to a spontaneous genetic mutation, which is not detected by prior testing.

In recent years, many severe hemophilia patients with AIDS have died. Depending on the source of the information, however, it seems that the peak year of AIDS victims among hemophiliacs was 1995, so that the overall number of hemophilia patients began to grow thereafter.

Furthermore, the following factors contribute to the hemophilia population increase, although it remains relatively modest:

- Many prospective parents of a boy with hemophilia believe that the currently available products, especially the recombinant products, are safe and will allow their hemophilia son to lead a quasi-normal life. Therefore they do not cancel or delay a pregnancy. Some 40 to 60 babies are born with hemophilia A and 5 to 8 with hemophilia B each year.

- Hemophiliacs generally enjoy a longer life expectancy than ever before, regardless of whether they are HIV positive or not.

- Those hemophilia patients who have contracted AIDS have now access to better treatment, which extends their life expectancy.

Today, the standard treatment consists in prescribing the high purity (monoclonal-antibody-purified and recombinant) Factor VIII to the HIV negative patients, and intermediate-purity products to the HIV positive patients.

6.3) Organization of Hemophilia Care: Hemophilia Treatments Centers and Home Care Companies

Many hemophilia patients are affiliated to a local chapter of the National Hemophilia Foundation (NHF). A CDC study reported that up to 37% did not obtain treatment from an HTC during a two year period. They were most likely mild hemophiliacs. The chapters provide educational and family support. At the national level, the NHF advocates for the hemophilia community and was instrumental in obtaining the votes in favor of the "Ricky Ray Fund Act" in October 1998 to compensate families victims of AIDS caused by clotting factors in the 1980's. In recent years, the NHF has taken upon itself to defend the interests of patients with von Willebrand's Disease (vWD).

In 1993, the "Committee of Ten Thousand" (COTT) was founded to represent hemophilia patients who had developed AIDS through clotting

factors. Since the financial problems have been essentially resolved, COTT has lost much of its influence.

Another organization, the "Coalition for Hemophilia B Patients" defends the interests of this group of patients.

An estimated 60% of the severe and moderate hemophiliacs are affiliated with a home care company. These companies supply patients on home treatment with clotting factors. They generally offer other services, such as reimbursement assistance, family support, summer camps, educational activities, provision of ancillary supplies and drugs, etc. The largest home care companies are Caremark Therapeutic Services with an estimated 2,500 patients, "Gentiva Health Services" (about 2,000 to 2,400 patients, "Hemophilia Health Services" or "HHS" with some 1,200 patients. Other home care companies include the "American Home Federation", or "AHF", with an estimated 330 patients), and several home care companies which are a subsidiary of a distribution company. "NuFactor" (240 patients, subsidiary of FFF Enterprises), "Apex" (80 patients subsidiary of Actsys Medical, recently sold), "ASD Direct" (50 patients subsidiary of ASD, itself a subsidiary of Bergen Brunswig, also recently sold), etc. Many new, small sized home care companies are created every year, serving the need of a few dozen patients, usually confined to a city or small geographic area.

The home care sector underwent a series of mergers and acquisitions in 2001. They were attributed to the difficulty for these companies to be profitable with declining reimbursement rates by insurance companies and higher acquisition prices for clotting factors. Furthermore, the small home care companies experienced difficulties in obtaining clotting factors from the manufacturers, which served larger customers first.

In 2001, Hemophilia Health Services (HHS) and its recent acquisitions "Nova Factor" and "Sunrise Health Management" were acquired by "Accredo Health". Later in the year, Accredo Health acquired "Biopartners in Care". In early 2002, "Gentiva Health Services" announced that its Specialty Pharmaceutical Services – which serves

the hemophilia and IVIG communities – would also be acquired by Accredo Health. To better streamline its home care activities, Accredo split the hemophilia and the IVIG sectors: Sunrise Health Management, "Pharmacare Resources of America", and a new company to be created as a result of the acquisition of Gentiva's IVIG business would focus on IVIG therapy while the others will continue serving the hemophilia community. Two other important players in the hemophilia home care field are:

- Curative Health Services, Inc which acquired e-BioCare, Hemophilia Access and, recently, Apex Therapeutics Care, and
- Priority Health Care's specialty pharmacy business which acquired the largest home care company in Florida, Hemophilia of the Sunshine States and is poised to further expand.

Both "ASD Direct" and "APEX", tow home care companies affiliated with distributors of plasma products were sold in 2001 or 2002.

In general, a smooth relationship exists between the treatment center and the home care company because each of them maintains a well defined role, the former taking care of the medical aspects of the treatment, and the latter the procurement side, as well as other personal services, such as reimbursement assistance. Several home care companies employ hemophiliacs, as a way to support the hemophilia community and to provide jobs to individuals who often cannot find employment easily. Furthermore, by employing individuals who are familiar with the needs of their customers, they are more effective.

In recent years, statewide programs comparable to home care services have emerged, for example in Colorado, Georgia and Texas. Similar to home care companies, these programs offer drop-shipment of clotting Factors, telephone help-line, and ancillary services. As they are not-for-profit and are entitled to discounted "Public Health Service" pricing, these programs usually offer coagulation factors at a lower cost than the home care companies.

6.4) Historical Impact of Recombinant Clotting Factors

6.4.1) FACTOR VIII CONCENTRATES

In December 1992, the first coagulation Factor VIII concentrate made through recombinant DNA technology was licensed in Sweden and in the United States. "Recombinate", made by Genetics Institute and distributed by Baxter was the first non plasma-derived product available to hemophilia patients. Bayer's "Kogenate" was approved in February 1993 in the United States. Both products became available in Germany and other European countries a few months later on a compassionate basis. Recombinate was approved in July 1993 by the German Health Ministry, and Kogenate in April 1994. During the same year, both products were approved in virtually all the other European countries while the approval of Kogenate occurred later in Japan.

When recombinant products appeared on the market, a few patients switched immediately, in particular the "previously untreated patient" (PUPs) and the young, HIV negative hemophiliacs but the majority of hemophilia-treating physicians adopted a cautious attitude towards the product because of the good safety record of the existing concentrates, in particular the monoclonal antibody-purified products, and because the clinical trials had suggested that recombinant Factor VIII triggered the development of inhibitors in young hemophiliacs to a larger extent than did the plasma-derived products.

The market penetration of recombinant Factor VIII concentrates was somewhat slow at the beginning. However, product sales increased gradually and by the end of 1993, about 16.5% of all the hemophilia A patients were using either Kogenate or Recombinate At the beginning of 1994, Centeon/Armour introduced "Bioclate" and "Helixate" which were Baxter's and Bayer's products respectively sold under different brand names. As a result of the patent litigation between these companies, Centeon/Armour had obtained the right to distribute these recombinant products under its own label.
As the acceptance of the recombinant Factor VIII products increased further, more patients converted from plasma-derived products, including older and HIV seropositive hemophilia patients. By the end of

including older and HIV seropositive hemophilia patients. By the end of 1994, close to 37% of all hemophilia A patients had adopted a recombinant Factor VIII concentrate in the United States. The trend continued to reach nearly 60% at the end of 1997, and to plateau to 78% at the end of 1998. Today, the percentage is about the same, due to the shortages of recombinant Factor VIII. It would have probably increased if more product was available.

In 1998, Baxter announced the FDA approval of its a new plant at Thousand Oaks, California, capable of increasing the supply of Recombinate by 40%. Since 2000, Baxter no longer supplies Aventis Behring with Bioclate although some sales were recorded in early 2001.

In 2000, Bayer introduced "Kogenate SF" (Sucrose Formulated), a second-generation recombinant Factor VIII concentrate formulated with sucrose as stabilizer instead of albumin. Bayer was also reported to be working on a new rFVIII in which all human and animal protein components used in the manufacturing process would be removed.

Bayer initially indicated that "Kogenate SF" would be distributed exclusively through its "Bayer Direct" program to hemophilia patients, bypassing distributors and home infusion companies. Through this program, Bayer's intention was to relieve the rFVIII shortage by eliminating excess inventories held by home therapy companies, hospitals and distributors. Late in 2000, under the pressure of the patients' groups, Bayer rescinded its decision to require hemophilia patients to join "Bayer Direct" in order to obtain "Kogenate SF."

In March 2000, Wyeth's "ReFacto" received FDA approval in the United States, and the product was launched in January 2001. ReFacto is devoid of the B-domain of the Factor VIII molecule. Furthermore, it is the first rFVIII product formulated without human albumin as a stabilizer, which characterize the "second generation" concentrates.

Genetics Institute purchased the development and commercialization rights to ReFacto from Pharmacia & Upjohn AB (now called "Biovitrum") in 1997. Under this agreement, Biovitrum manufactures

ReFacto which is sold by Wyeth (formerly "American Home Products") in the U.S. and most of the rest of the world.

6.4.2) FACTOR IX CONCENTRATES

In February 1997, Genetics Institute received FDA approval for "BeneFIX", its recombinant Factor IX concentrate. It does not contain any albumin as a stabilizer, and the manufacturing process does not contain any albumin in the growth medium. Taking advantage of the shortages of both Monoclate P and AlphaNine SD in early 1997, BeneFIX captured a substantial market share rapidly, to reach about 74% in 1998, and was 79% in 2001 (in dollars).

Virtually every "PUP" (Previously Untreated patient) born in the United States since the introduction of recombinant Factor VIII or IX has been prescribed such a product since these products became available, starting a new generation of hemophilia patients who will normally not use any plasma-derived product during their lifetime.

6.5 Gene Therapy

For patients and physicians, gene therapy is the ultimate goal of hemophilia treatment. Although gene therapy may only reduce the severity of hemophilia instead of curing it, it fully justifies the current Research & Development efforts.

Transkaryotic Therapies (TKT)

Transkaryotic Therapies (TKT) initiated the first clinical trial at the end of 1998, using a "ex vivo" technology: according to the protocol, skin cells are taken from the patient; hemophilia A genes are inserted into these cells, and they are subsequently returned to the patient, ready to produce the missing Factor VIII. The trial was temporarily halted in February 2000 following the death of a young individual who was treated at another center with gene therapy for a different kind of disease (Ornithine Transcarbamylase, OTC) caused by a deficiency of a liver enzyme, unrelated to hemophilia. In mid-2001, reports of patients undergoing gene therapy for almost a year were published, suggesting that the procedure was at least safe, and possibly efficacious.

Targeted Genetics Corporation

In early 2001, Wyeth/Genetics Institute and Targeted Genetics Corp. entered into a collaborative agreement for the use of the former's adeno-associated virus technology to deliver Genetics Institute's Factor VIII in development.

GenStar Therapeutics

GenStar Therapeutics is conducting a Phase I gene therapy clinical trial for the treatment of hemophilia A, using the company's viral gene delivery system called "Maximum-AD". The multicenter trial follows studies in animal models, which demonstrated sustained therapeutic levels of Factor VIII. Developed in collaboration with Baxter Healthcare, the Maximum-AD gene delivery platform utilizes the common cold adenovirus, from which all viral genes have been removed to permit the maximum capacity for delivery of the therapeutic gene. Late in 2001, The trial was briefly interrupted after it was discovered that the first patient developed temporary blood coagulation and laboratory liver function abnormalities.

Avigen

Avigen, a company based at Stanford University, California, developed a product called "Goagulin B" which enables the production of Factor IX when administered to the patient by intramuscular route. This procedure is in Phase I/II clinical trial. In late 2001, the trial was briefly suspended because a trace amount of DNA from the adeno-associated virus vector carrying the Factor IX gene was detected in the seminal fluid of the first patient in the trial. Avigen signed an exclusive agreement with Bayer granting the latter worldwide marketing and distribution rights in exchange of several payments totaling about $60 million. Bayer will assist in conducting late-phase clinical trials, and take part in the regulatory approval processes in the U.S. and elsewhere.

Other companies, in particular Chiron and Pharming Healthcare have abandoned their efforts in the gene therapy area.

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

PLASMA-DERIVED FACTOR VIII (HEMOPHILIA A MARKET)

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00 UNITS	CHANGE FROM '00 DOLLARS	SHARE IN UNITS	PRICE CHANGE
Aventis Behring	95	0.55	52.250	6.9%	11.8%	19.4%	8.0%	0.04
Baxter	165	0.49	80.025	10.6%	57.1%	63.9%	13.8%	0.02
American Red Cross	190	0.37	70.300	9.3%	72.7%	72.7%	15.9%	-
Total	450	0.45	202.58	26.8%	50.0%	52.0%	37.7%	

* International Units

RECOMBINANT FACTOR VIII (HEMOPHILIA A MARKET)

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00 UNITS	CHANGE FROM '00 DOLLARS	SHARE IN UNITS	PRICE CHANGE
Baxter	610	0.72	439.200	58.2%	23.2%	30.5%	51.1%	0.04
Bayer	38	0.90	34.200	4.5%	-57.8%	-53.7%	3.2%	0.08
Wyeth	40	0.80	32.000	4.2%	N.A.	N.A.	3.4%	0.07
Aventis Behring	55	0.85	46.750	6.2%	-54.2%	-46.6%	4.6%	0.12
Total	743	0.74	552.150	73.2%	5.4%	10.9%	62.3%	

* International Units

TOTAL HEMOPHILIA A MARKET

COMPANY	UNITS * (MM)	DOLLARS (MM)	MARKET SHARE	UNITS CHANGE	DOLLARS CHANGE
Aventis Behring	150	99.000	13.1%	-26.8%	-24.6%
Baxter	775	519.225	68.8%	29.2%	34.7%
American Red Cross	190	70.300	9.3%	72.7%	72.7%
Wyeth	40	32.000	4.2%	-55.6%	-56.6%
Bayer	38	34.200	4.5%	-57.8%	-53.7%
Total	1,193	754.725	100.0%	18.7%	10.6%

* International Units

THE FACTOR VIII CONCENTRATE MARKET IN THE UNITED STATES
$ MILLION

	1980	1982	1984	1986	1988	1990	1992	1994	1995	1996	1997	1998	1999	2000	2001
PLASMA-DERIVED															
AVENTIS BEHRING	6.5	13.2	12.0	11.1	66.2	65.1	75.4	79.1	79.3	77.6	34.5	19.6	65.1	91.0	52.2
BAXTER	9.8	10.4	14.4	14.3	66.0	64.1	73.1	73.2	63.8	54.2	52.5	47.3	50.4	48.8	80.0
BAYER	18.9	17.5	13.1	15.0	33.7	32.3	21.2	19.5	12.6	10.1	11.5	9.0	8.6	7.4	-
RED CROSS	2.1	3.5	5.7	6.8	51.6	49.0	59.6	20.6	27.2	33.1	33.0	45.1	40.7	40.7	70.3
ALPHA	4.5	6.0	8.2	7.1	16.6	21.4	15.6	7.0	7.7	10.6	11.9	6.0	5.8	2.3	-
ALL OTHERS	0.2	-	0.3	0.5	16.9	16.7	11.7	14.6	13.4	-	-	-	-	-	-
SUB TOTAL	42.0	50.6	53.7	54.8	251.0	248.6	256.6	214.0	204.0	185.6	143.4	127.0	170.6	190.2	202.5
RECOMBINANT															
BAXTER	-	-	-	-	-	-	-	95.0	111.8	139.4	144	172.8	304.5	336.6	439.2
BAYER	-	-	-	-	-	-	-	53.3	44.9	58.1	67.2	109.8	75.6	73.8	34.2
AVENTIS BEHRING	-	-	-	-	-	-	-	2.3	16.1	24.1	62.0	93.0	80.4	87.6	46.7
WYETH	-	-	-	-	-	-	-	-	-	-	-	-	-	-	32.0
SUB TOTAL	-	-	-	-	-	-	-	150.6	172.8	221.6	273.2	375.6	460.5	498.0	552.1
TOTAL MARKET	-	-	-	-	-	-	-	364.6	376.8	407.2	416.6	502.6	631.1	688.2	754.6

Market Conversion to New Factor VIII Products - 1985 to 2001
In Units and Price per International Unit

	1985	1986	1987	1989	1990	1992	1994	1996	1998	1999	2000	2001
Non Heat-Treated												
Units (Million)	15	-	-	-	-	-	-	-	-	-	-	-
Average Price ¢	7.0											
Dry Heat-Treated												
Units (Million)	540	577	559	75	-	-	-	-	-	-	-	-
Average Price ¢	10.3	9.5	9.5	18.0								
Wet Heat-Treated												
Units (Million)	-	-	27	77	25	12	-	-	-	-	-	-
Average Price ¢	-	-	25.9	38.3	49.6	75.0	-	-	-	-	-	-
Monoclonal-Antibody Purified												
Units (Million)	-	-	5	335	320	397	307	326	223	287	300	450
Average Price ¢	-	-	55.4	54.8	54.8	52.4	59.5	47.6	42.7	43.0	44.0	45.0
Intermediate Purity												
Units (Million)	-	-	-	72	185	169	108	89	40	75	99	86
Average Price ¢	-	-	-	34.0	31.3	23.4	28.5	23.2	37.5	62.2	58.2	95.0
Total Plasma Market												
Units (Million)	555	577	591	559	535	578	415	415	263	362	399	536
Average Price ¢	10.6	9.5	10.6	44.9	46.4	44.4	53.9	44.7	42.8	47.1	47.7	45.0
Recombinant												
Units (Million)	-	-	-	-	-	-	203	332	586	663	705	743
Average Price ¢	-	-	-	-	-	-	74.0	66.7	64.1	69.0	71.0	74.0
Total Market												
Units (Million)	555	577	591	559	535	578	618	747	849	1,025	1,104	1,279

THE FACTOR VIII/vWD CONCENTRATE MARKET IN THE UNITED STATES

(In Million International Units)

	1994	1995	1996	1997	1998	1999	2000	2001
PLASMA-DERIVED								
AVENTIS BEHRING	137	130	121	55	50	65	85	95
BAXTER	122	112	113	125	110	112	105	165
BAYER	65	45	46	50	25	20	18	11
RED CROSS	48	68	92	100	110	110	110	190
ALPHA THERAPEUTIC	28	24	33	35	15	15	6	30
ALL OTHERS (vWD)	16	14	10	8	3	40	42	45
SUB TOTAL	416	393	415	373	313	362	366	536
RECOMBINANT								
BAXTER	125	162	208	225	290	435	495	610
BAYER	75	66	88	105	166	108	90	38
AVENTIS BEHRING	3	24	36	100	160	120	120	55
WYETH	-	-	-	-	-	-	-	40
SUB TOTAL	203	252	332	430	616	663	705	743
TOTAL MARKET	619	645	747	803	929	1,025	1,071	1,279

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THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

TOTAL VON WILLEBRAND'S DISEASE MARKET

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00 UNITS	CHANGE FROM '00 DOLLARS	SHARE IN UNITS	PRICE CHANGE
Bayer	11	0.42	4.620	0.6%	-38.9%	-37.4%	0.9%	0.01
Alpha Therapeutic	30	0.40	12.000	1.4%	400.0%	412.8%	2.3%	0.01
Aventis Behring **	45	1.44	64.800	7.7%	7.1%	22.4%	3.5%	0.13
Total Factor VIII units	86	0.95	81.420	9.7%	30.3%	30.0%	6.7%	

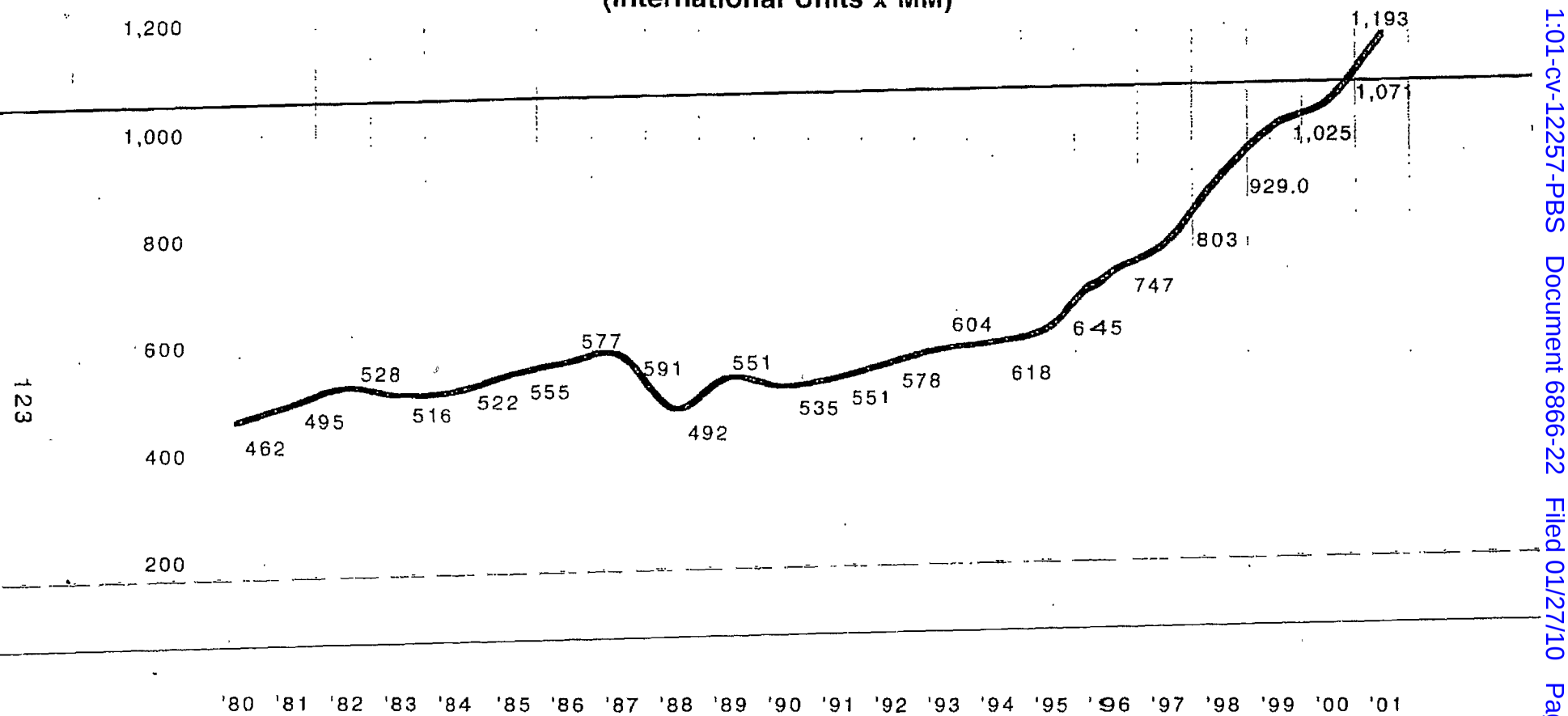
* International Units of Factor VIII

** Humate P sales, expressed in Factor VIII Units, and equivalent to 165 million Ristocetin CoFactor Units @ $0.72 per Risto. Unit

Total VWD market in Ristocetin co-Factor Units (million): 128.0

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

THE FACTOR VIII MARKET FROM 1980 TO 2001
(International Units x MM)



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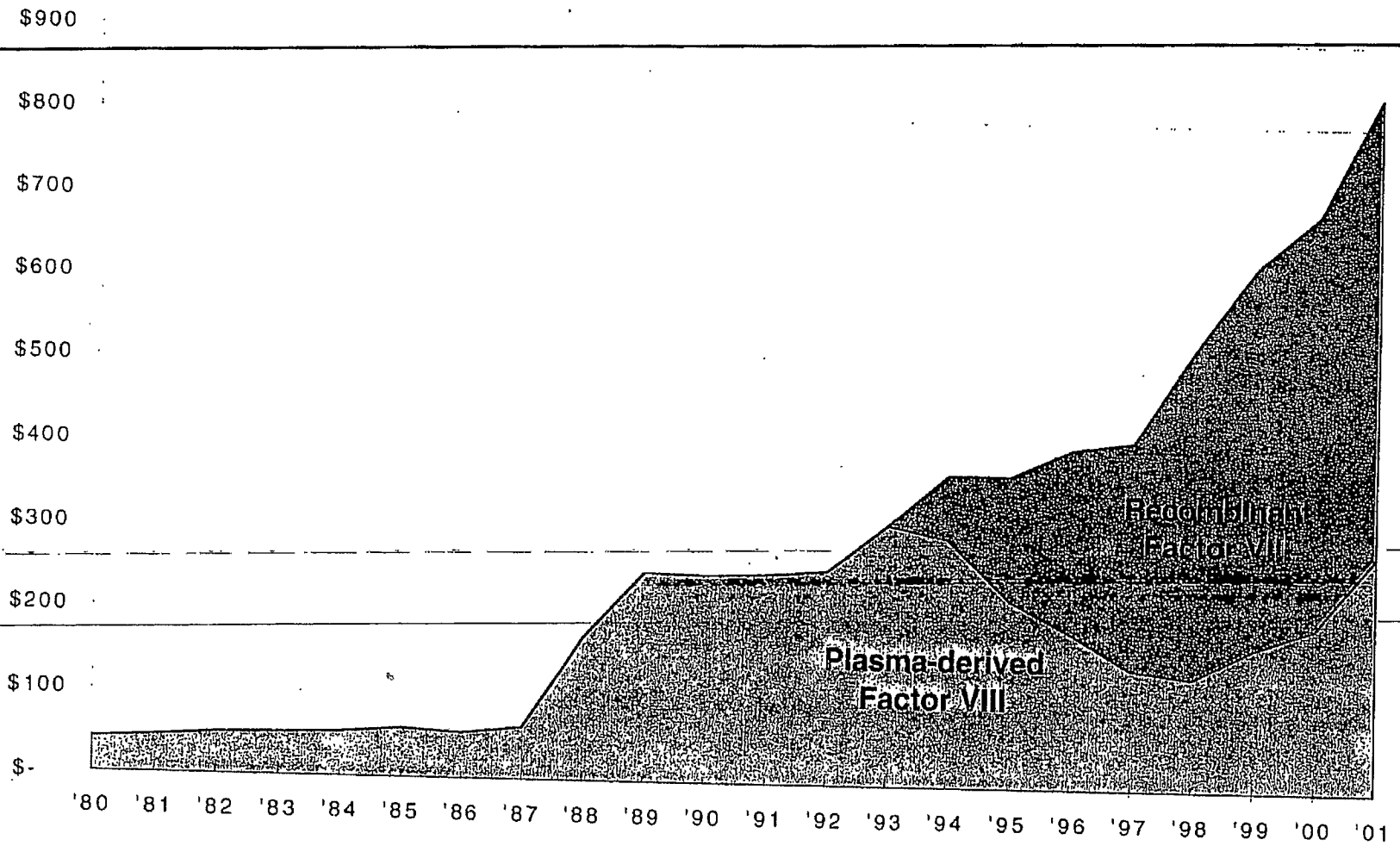
THE FACTOR VIII MARKET FROM 1980 TO 2001
SALES IN DOLLARS (MM)



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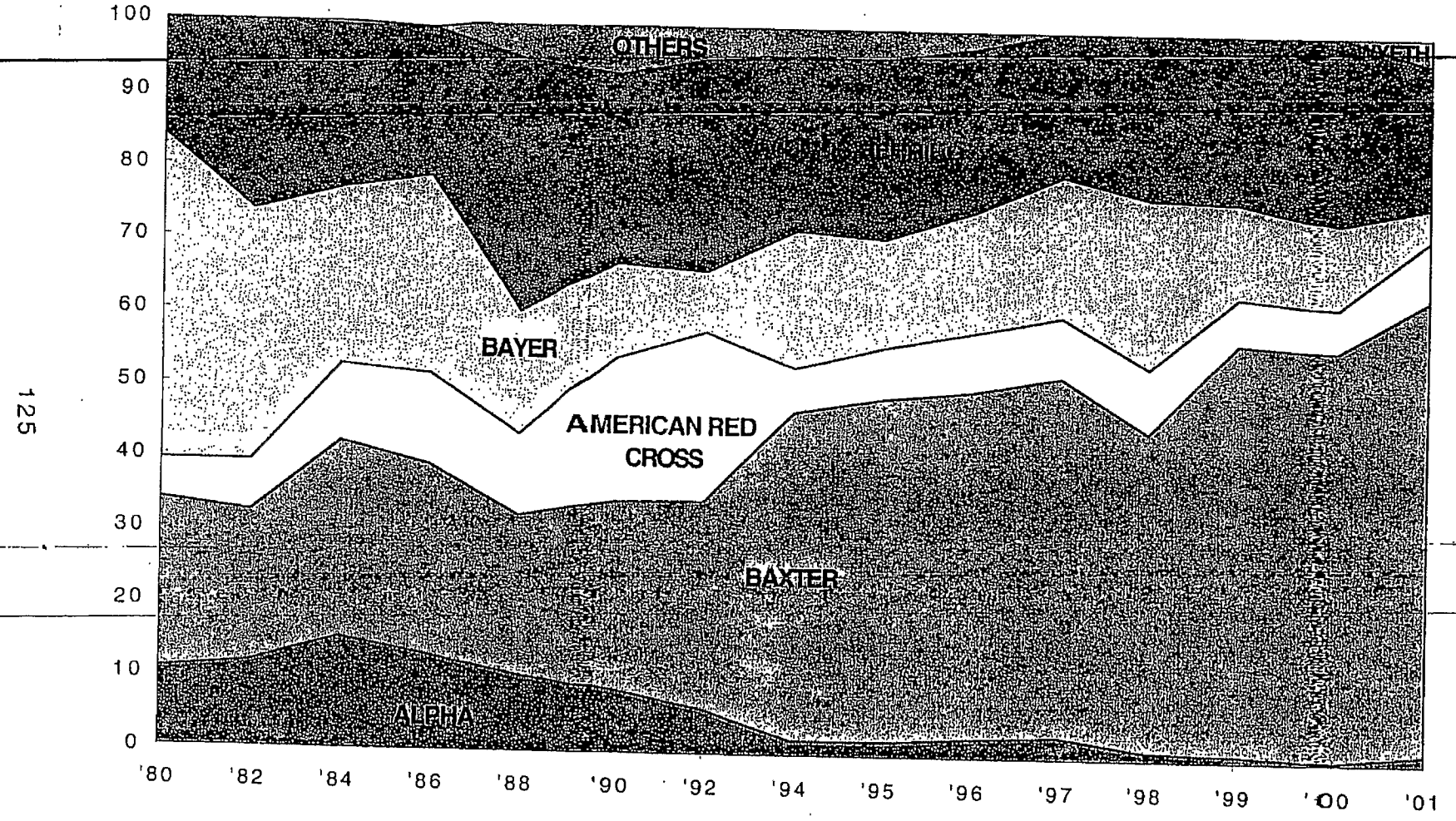
THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

THE FACTOR VIII MARKET FROM 1980 TO 2001
Market Shares Based on Sales in Dollars - including rFVIII & VWD



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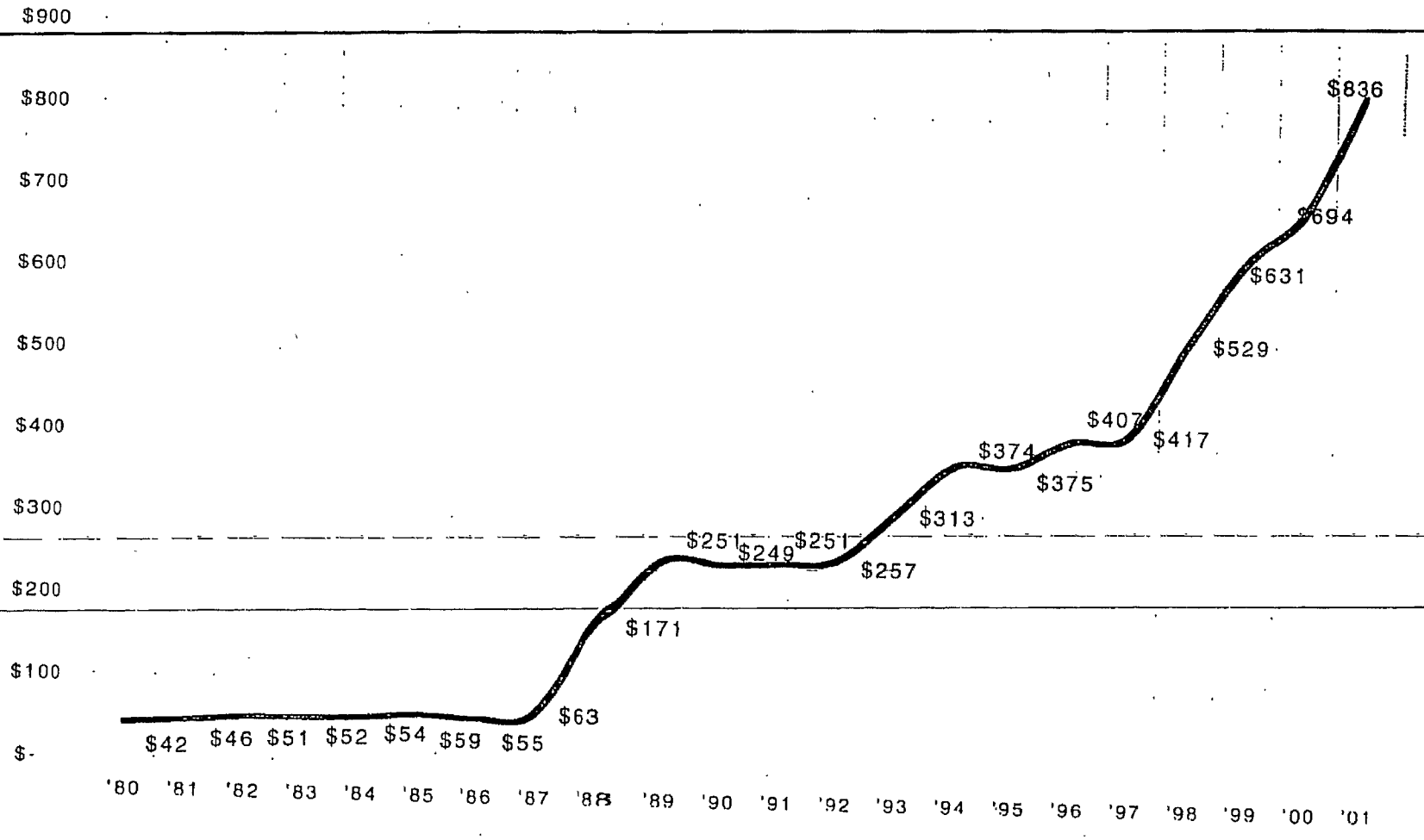
FACTOR VIII
PRICE PER INTERNATIONAL UNIT
PLASMA-DERIVED PRODUCTS

YEAR	PRICE/UNIT	CHANGE
1980	9.1¢	- 1%
1981	9.2¢	+ 1%
1982	9.6¢	+ 4%
1983	10.0¢	+ 4%
1984	10.3¢	+ 3%
1985	10.6¢	+ 3%
1986	9.5¢	- 10%
1987	10.6¢	+ 12%
1988	34.7¢	+227%
1989	44.9¢	+ 29%
1990	46.4¢	+ 3%
1991	45.5¢	- 2%
1992	44.4¢	- 2%
1993	47.9¢	+ 8%
1994	54.0¢	+ 13%
1995	51.9¢	- 4%
1996	45.0¢	- 13%
1997	38.4¢	- 14%
1998	43.0¢	+ 12%
1999	46.0¢	+ 7%
2000	36.6¢	- 11%
2001	45.0¢	+ 50%

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

THE FACTOR VIII MARKET IN THE UNITED STATES FROM 1980 TO 2001
(Dollars X MM)



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6.6) FACTOR VIII MARKET

6.6.1) MARKET DEVELOPMENTS

In 2001, the Factor VIII market was worth $836.1 million. Factor VIII concentrate is prescribed to two different indications – hemophilia A and von Willebrand's Disease - each corresponding to a specific sub-market:

a) The Factor VIII deficiency market (hemophilia A) is served by clotting factors featuring a high Factor VIII activity but no or low von Willebrand Factor. This includes the recombinant Factor VIII concentrates (Recombinate, Kogenate, Helixate, and ReFacto), and the monoclonal antibody-purified (Hemofil M, Monarc M and Monoclate P) Factor VIII concentrates. Some of the "intermediate purity" Factor VIII products are also prescribed to a small number hemophilia A patients.

b) The von Willebrand Factor Disease market is served by one products which is FDA-approved for this indication since 1999: Aventis Behring's "Humate P", and by two non FDA-approved "intermediate purity" products, Alpha Therapeutic's "Alphanate" and Bayer's "Koate DVI", both of which have the von Willebrand cofactor, and a comparatively lower Factor VIII:c activity than those in the previous group.

When combining the above two categories, the total market (plasma-derived and recombinant) reached almost 1.3 billion units in 2001. The market was summarized as follows:

Sub-Market	Units (2001)	Change 2001/2000
1) Recombinant Factor VIII	743 million	+5.4%
2) monoclonal antibody-purified Factor VIII	450 million	+19.6%
Total Hemophilia A Market	1,193 million	+18.7%
3) Intermediate purity Factor VIII	86 million	+9.7%
Total von Willebrand's Disease Market	86 million	+9.7%
Total Factor VIII units	1,279 million	+19.4%

* In previous years, Humate P was expressed in Ristocetin co-Factor units

The Factor VIII market experienced a sharp increase between 2000 and 2001, as some 208 million units were added to the market, 188 million units to the hemophilia A market alone. The increase might have been even higher, had Kogenate FS not been in short supply, although the ample supply of plasma-derived products partially compensated for the shortfall of the recombinant products.

Soon after its launch, "Kogenate SF" suffered repeated manufacturing difficulties. Through 2001 Bayer issued sporadic lots of the product, and normal production level were gradually attained through 2002. However, the shortage of rFVIII forced many hemophilia A patients to switch back to a plasma-derived product, or to postpone or cancel surgeries, or to delay or give up prophylaxis or immune tolerance. Neither Recombinate nor ReFacto were available in sufficient quantities to offset the shortfall of Kogenate FS and Helixate FS. In general, the causes of the growth in volume of the Factor VIII market were:

- The young patients who began to use rFVIII eight years ago have gained weight and use substantially larger quantities of clotting factors,

- Hemophilia patients, in particular the young ones, treat themselves prophylactically more frequently and easily than before,

- The insurance companies reimburse recombinant Factor VIII more easily than before, and they cover prophylaxis because they recognize its long term medical, financial, social and economic advantages,

- Immune tolerance induction is more popular than it used to be because of a recognition of its long term benefits,

- Primary prophylaxis is more frequently prescribed by hemophilia-treating physicians. The risk of infection linked with the usage of a catheter or of a similar infusion device is now well controlled,

- The perceived and real safety of the clotting Factors allows hemophilia patients and their treating physicians to undergo surgeries more easily than a few years ago,

- The number of hemophilia patients dying from AIDS has stabilized, or possibly gone down. New AIDS treatments have become available prolonging the life of HIV-positive hemophilia patients,

- Prospective parents of a child with hemophilia know that he can lead a relatively normal and long life,

- The patients with low level inhibitors, in particular among those using recombinant Factor VIII, are treated with large doses of product to overwhelm the inhibitor.

In 2001, the market share of recombinant Factor VIII concentrate was 66.0% in dollars (6.4 percentage points less than in 2000) and 58.1% in units (5.8 percentage points less). This contrasted with previous years, when the usage of plasma-derived Factor VIII declined while the use of rFVIII increased.

When including the recombinant Factor VIII products, Baxter remained the market leader with 62.1% of total sales (+6.1 percentage points from the previous year). Aventis Behring followed with 19.6%. The American Red Cross was in third position with 8.4% market share. When considering only the plasma-derived concentrates, Baxter held close to

39% of this sub-market, the ARC, close to 35%, and Aventis Behring, the remaining 26%. Sales of ARC's "Monarc M" advanced the most among all the clotting factors, growing by 73% in one year. Baxter's sales of "Hemofil M" also rose sharply (+64%). Conversely, the sales of Kogenate FS and Helixate FS fell by 50% to 60% between 2000 and 2001. Recombinate sales increased by 23% in units and by 31% in dollars.

6.6.2) PRICING TRENDS

Between 2000 and 2001, clotting factor prices remained relatively stable. On average, the prices of plasma-derived products increased by 2¢ to 4¢, and those of recombinant products, by 4¢ to 12¢. The difference in price per unit between the least expensive recombinant product (Recombinate) and the most expensive plasma-derived Factor VIII product (Monoclate P) was 17¢ (72¢ and 55¢ respectively).

Over the years, the price of the monoclonal antibody-purified products declined in order to remain competitive against recombinant Factor VIII, and the price of the "intermediate purity" products declined to remain competitive against the monoclonal antibody-purified products. A survey conducted among fifty treatment centers across the country showed the regular downward trend in the acquisition prices of the various coagulation factors from 1994 to 1999, and the increase for many of them by early 2000:

Average Acquisition Prices per International Unit
From 1997 to 2001

	01/97	01/98	01/99	01/00	01/01	03/02
Kogenate (not SF)	71¢	66¢	64¢	66¢	70¢	N.A.
Recombinate	76¢	65¢	64¢	64¢	70¢	72¢
Helixate	76¢	67¢	61¢	62¢	65¢	N.A.
Monarc - M	42¢	36¢	33¢	41¢	37¢	35¢
Hemofil M	61¢	48¢	41¢	43¢	47¢	49¢
Monoclate P	65¢	57¢	50¢	49¢	51¢	55¢
Koate DVI	53¢	25¢	25¢	36¢	43¢	42¢
Alphanate	32¢	32¢	34¢	40¢	39¢	40¢
BeneFIX	N.A.	N.A.	71¢	71¢	73¢	74¢
AlphaNine SD	59¢	55¢	55¢	54¢	47¢	57¢
Mononine	73¢	71¢	69¢	66¢	68¢	70¢
Profilnine SD	13¢	19¢	17¢	21¢	29¢	29¢
Proplex T	16¢	15¢	14¢	17¢	19¢	27¢
Bebulin VH	33¢	26¢	22¢	22¢	26¢	29¢
Feiba VH	77¢	78¢	75¢	86¢	81¢	1.05¢
Autoplex T	85¢	86¢	69¢	87¢	74¢	80¢
Hyate:C	$ 1.15	$ 1.33	$ 1.25	$1.65	$1.59	$1.24
Humate P *	$ 1.04	$ 0.95	$ 0.87	$0.96	67¢	72¢

* Factor VIII units. From 2000 on, Humate P was priced according to its "Ristocetin co-Factor".

Through 2000, the price of cryoprecipitate was $1,400 per kilogram (40,000 international units) and up.

In November 1992, a "Veterans Health Care Act" was signed as Public Law 102-585, which enacted Section 340B of the Public Health Service Act entitled "Limitation on Prices of Drugs Purchased by Covered Entities". According to this Act, a manufacturer who sells selected drugs (including coagulation factors) to "eligible" entities (institutions partially or entirely financed by grants from the Federal Government) must sign a pharmaceutical pricing agreement with the

Secretary of Health and Human Services whereby the manufacturer agrees to charge a price for covered outpatient drugs that will not exceed the average manufacturer price decreased by a rebate percentage.

For many treatment centers, this was an opportunity to obtain substantial discounts on clotting factors. The intent of this law was to help the hospitals caring for indigent patients, including many hemophiliacs who could not afford the cost of clotting factors, and operating with federal money to ease their financial burden. The discount was not aimed to be necessarily passed on to the hemophilia patients although most of the centers did so.

According to this text, each manufacturer of clotting factor must supply pricing information and provide quarterly rebates to Health and Human Services reflecting the difference between the "average manufacturer's price" (AMP) and the "best price", or 12.5% of the AMP, whichever was greater.

At the beginning of 2001, about 45 hemophilia treatment centers had taken advantage of the VA bill, which has been the main contributing factor to the decline of the price of clotting factors since 1993.

Since this bill requires detailed record keeping on product usage and patient profiles by the treatment centers, some of them consider that it requires an excessive administrative burden, and explains why not all of the centers have adopted it.

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

"PURE" FACTOR IX

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00	
					UNITS	DOLLARS
Aventis Behring	43	0.70	30.100	62.3%	22.9%	26.5%
Alpha Therapeutic	32	0.57	18.240	37.7%	300.0%	385.1%
Total	75	0.64	48.340	100.0%	70.5%	72.5%

* International Units

FACTOR IX COMPLEX

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00	
					UNITS	DOLLARS
Alpha Therapeutic	2	0.29	0.580	41.7%	0.0%	-1.7%
Baxter	3	0.27	0.810	58.3%	-25.0%	-8.0%
Total	5	0.28	1.390	100.0%	-16.7%	-5.4%

* International Units

RECOMBINANT FACTOR IX

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00	
					UNITS	DOLLARS
Wyeth	180	0.74	133.200	72.8%		
Total	180		133.200	72.8%	-7.3%	-6.1%

* International Units

TOTAL RECOMBINANT AND PLASMA DERIVED FACTOR IX AND FIX COMPLEX

COMPANY	UNITS * (MM)	DOLLARS (MM)	MARKET SHARE	UNITS CHANGE	DOLLARS CHANGE
Wyeth	180	133.200	72.8%	-7.3%	-6.1%
Baxter	3	0.810	0.4%	-25.0%	-8.0%
Alpha Therapeutic	34	18.820	10.3%	240.0%	332.6%
Aventis Behring	43	30.100	16.5%	22.9%	26.5%
Total	260	182.930	100.0%	6.4%	6.8%

* International Units

THE FACTOR IX CONCENTRATE MARKET IN THE UNITED STATES
$ MILLION

	1980	1984	1986	1988	1990	1991	1993	1994	1995	1996	1997	1998	1999	2000	2001
PLASMA-DERIVED															
GENETICS INSTITUTE	-	-	-		-	-	-	-	-	-	49.0	85.2	135.0	141.8	-
ALPHA	-	0.9	2.3	3.6	3.1	13.7	27.8	29.0	29.8	30.1	32.5	27.8	9.8	4.3	18.8
BAYER	47.6	5.7	6.8	6.9	4.3	4.1	7.2	6.5	4.8	4.8	4.8	2.6	-	-	-
BAXTER	3.2	4.3	2.7	2.5	2.0	1.8	1.2	0.5	0.5	0.3	0.3	1.3	1.0	0.9	.8
AVENTIS BEHRING	-	0.5	-	-	-	-	39.5	36.2	41.4	51.8	19.3	3.3	17.0	23.8	30.1
RED CROSS	-	-	0.6	0.4	0.6	.5	0.5	2.9	2.8	5.3	4.0	4.1	.94	.47	-
IMMUNO	-	-	-	-	-	-	0.8	1.3	1.3	1.6	1.3	-	-	-	-
SUB TOTAL ($ MILLIONS)	10.8	11.4	12.4	13.4	10.0	20.1	77.0	77.9	80.3	93.9	111.2	124.3	163.8	171.3	49.7
RECOMBINANT															
WYETH	-	-	-		-	-	-	-	-	-	-	-	-	-	133.3
SUB TOTAL	-	-	-		-	-	-	-	-	-	-	-	-	-	133.3
TOTAL MARKET ($ MILLIONS)	10.8	11.4	12.4	13.4	10.0	20.1	77.0	77.9	80.3	93.9	111.2	124.3	163.8	171.3	182.9
TOTAL MARKET (MILL. UNITS)	91	134	146	154	160	159	164	167	168	170	210	212	240	244	260

FACTOR IX CONCENTRATE
(INTERNATIONAL UNITS)

	MILLION	CHANGE
1980	91	
1981	102	+ 15%
1982	121	+ 12%
1983	129	+ 19%
1984	134	+ 7%
1985	145	+ 4%
1986	149	+ 8%
1987	157	+ 3%
1988	154	+ 5%
1989	150	- 1%
1990	159	- 3%
1991	162	+ 6%
1992	164	+ 2%
1993	167	+ 1%
1994	168	+ 2%
1995	170	+ 1%
1996	190	+ 1%
1997 *	210	+ 12%
1998	212	+ 11%
1999	240	+ 1%
2000	244	+ 13%
2001	260	+ 1.8%
		+ 6.4%

* Includes recombinant Factor IX from 1997

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FACTOR IX

AVERAGE SELLING PRICES

PLASMA-DERIVED ONLY

	PER UNIT	% CHANGE
1980	11.9¢	+ 5.0
1981	11.4¢	- 4.0
1982	11.0¢	- 4.0
1983	11.0¢	- - -
1984	8.5¢	- 22.8
1985	8.6¢	+ 1.2
1986	8.3¢	- 3.5
1987	8.0¢	- 3.6
1988	8.6¢	+ 7.0
1989	7.2¢	- 16.2
1990	6.3¢	- 12.5
1991	12.4¢	+ 96.8
1992	18.4¢	+ 48.4
1993	46.1¢	+150.5
1994	46.4¢	+ 1.1
1995	47.2¢	+ 1.7
1996	49.4¢	+ 4.6
1997	43.8¢	- 11.3
1998	42.5¢	- 3.0
1999	52.1¢	+ 23
2000	59.0¢	+ 13.2
2001	64.0¢	+ 10.8

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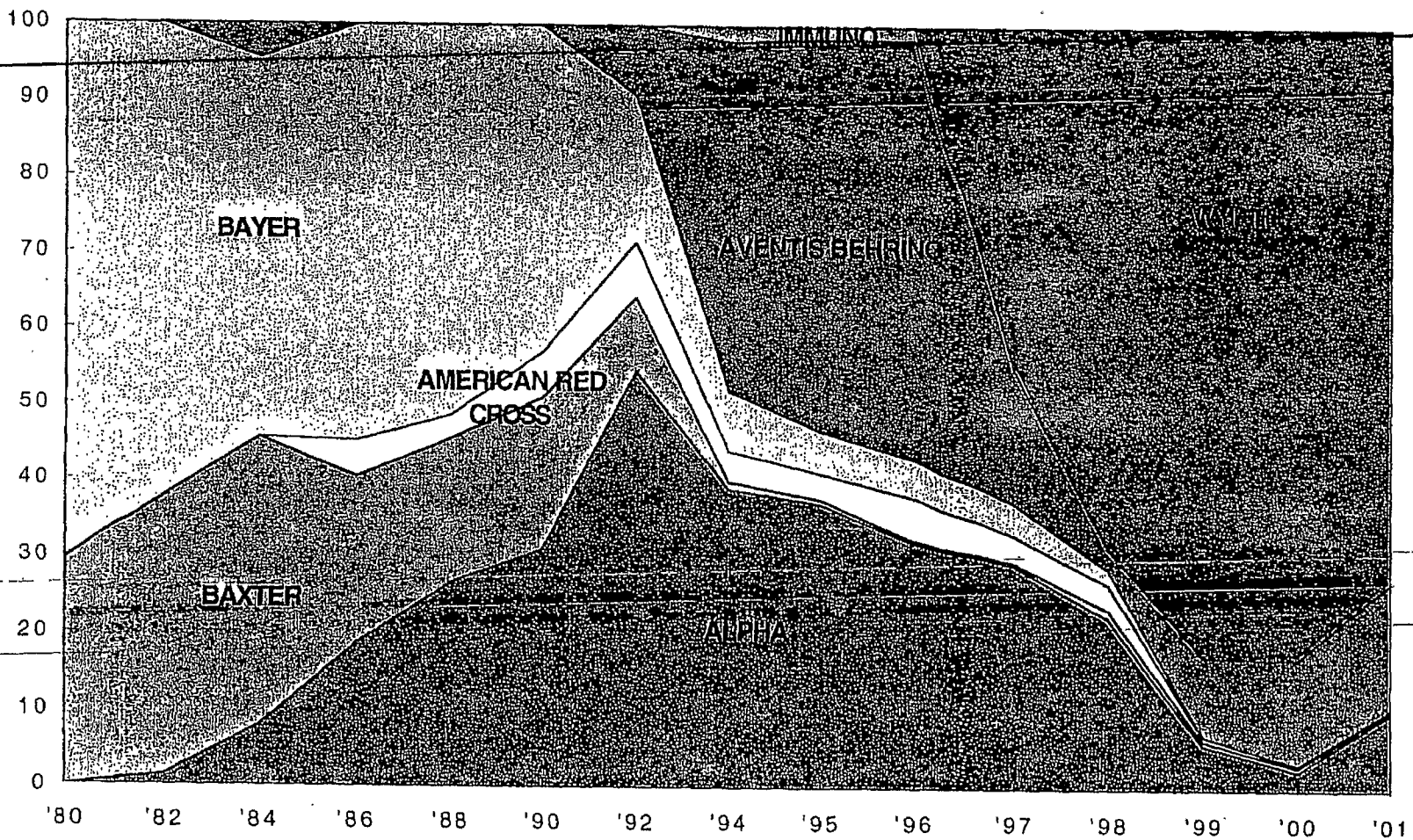
THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

THE FACTOR IX MARKET FROM 1980 TO 2001
Market Shares based on Sales in Dollars



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6.7) FACTOR IX MARKET

In 2001, the Factor IX market was worth $182 million. Between 2000 and 2001, it increased slightly (+6.4% in units, +6.8% in value). BeneFIX (recombinant Factor IX) maintained its leadership with 69.2% of the market in units (79.5% in 2000), and 72.8% in dollars, a ten percentage points drop from the previous year (82.8%), due to the advance of Mononine and AlphaNine SD. Aventis Behring increased its market share from 13.9% to 16.5% and Alpha Therapeutic from 2.5% to 10.3%, the strongest progression among all the plasma products.

Only five million units of Factor IX Complex concentrates, or "Prothrombin Complex concentrates ("PCC") were sold in 2001. This type of product has become virtually obsolete as it is used by a minority of mild hemophilia B patients, possibly by a few hemophilia A patients with inhibitors, and in surgery where it is administered to counter the anticoagulation effect of heparin or Coumadin which may lead to excessive bleeding. As Factor IX Complex concentrates may cause thromboembolic complications, especially when infused in large doses (e.g. in surgery), most Factor IX-deficient patients switched to the "pure" Factor IX products when they became available on the market in the early 1990's. AlphaNine was approved by the FDA in 1991, and Mononine in 1992.

In February 1997, Wyeth/Genetics Institute received FDA approval for "BeneFIX", its recombinant Factor IX concentrate. It does not contain any albumin as a stabilizer, and the manufacturing process does not involve the use of albumin in the growth medium. Wyeth (formerly American Home Products) sells "BeneFIX" in the U.S. with its own sales force of about 30 sales representatives - among the 100 who also detail "Neumega", the company's platelet growth Factor.

Higher doses of "BeneFIX" are often required in some patients to achieve the same hemostatic effect as the native human plasma-sourced Factor IX concentrates, in particular in surgery. While the growth of the Factor IX market is attributed to the same reasons as the Factor VIII market, this additional clinical factor is to be taken into account when analyzing the expansion of the Factor IX market in units.

6.8) VON WILLEBRAND'S DISEASE MARKET

The von Willebrand Disease (vWD) patients are categorized in three main groups:

- Type I: mild patients, who are not symptomatic except in situations where there is a loss of blood. This group makes up 80% to 90% of the von Willebrand's patients' population. No treatment is usually required for them.

- Type II: This group makes up 10% to 15% of the von Willebrand's patients' population and is divided into several subgroups. The Type IIB patients sometimes requires plasma-derived factor.

- Type III: Severe vWD patients, represent 1% to 1.5% of the patients' population, and often need vWD Factor replacement therapy.

In 2001, an estimated 86 million Factor VIII units of Humate P Alphanate, and Koate DVI were sold for a total of $81.4 million, a 30.3% increase from the previous year, both in units and dollars.

This progression was attributed to the efforts of National Hemophilia Foundation and its chapters, as well as of treatment centers, to identify, diagnose, and treat patients with vWD deficiency. In early 2000, the CDC reported 6,743 individuals suffering from vWD (severe).

Some 3.5 million people are believed to be affected by von Willebrand's Disease in the United States, while only 75,000 to 100,000 have been diagnosed. Almost every Hemophilia Treatment Centers (HTC) records a large number of patients registered with a mild form of von Willebrand's disease who need limited or no treatment. Von Willebrand's disease affects both males and females.

Aventis Behring's "Humate P" manufactured in Marburg, Germany, has traditionally been the product of choice to treat severe vWD because it has the most potent von Willebrand molecule among all the coagulation factors on the market. Its "Ristocetin cofactor" which measures the potency of the vWD molecule in a Factor concentrate is 2.2 for one unit

of Factor VIII in Humate P. In "Alphanate", this ratio is 0.5/1, and in Koate HP, 1/1. Alpha Therapeutic has sought FDA approval of Alphanate for this indication. Such approval is pending.

Since the recombinant Factor concentrates do not contain the von Willebrand's molecule, they cannot be used in the treatment of von Willebrand's disease. The monoclonal antibody-purified concentrate have a low "Ristocetin" cofactor which makes them unsuitable for vWD treatment either.

In 1991, "Stimate", an injectable formulation of Desmopressin acetate (DDAVP) was introduced by Aventis Behring for the treatment of mild-to-moderate Type I vWD and mild hemophilia A. It is not made from human plasma, and is the treatment of choice in treating mild and moderate Type I vWD, as well as some mild Factor VIII-deficient patients.

"Stimate" stimulates the release of Factor VIII and vWD Factor from their respective sites of synthesis and storage. In mild or moderate Hemophilia A, or vWD patients, a dose of DDAVP can triple the Factor VIII level. However, some normal Factor VIII must be present for the DDAVP to be effective. For this reason, severe Factor VIII/vWD deficient patients who lack the capacity to make normal Factor VIII must resort to other products, such as "Humate P".

In 1994, Aventis Behring introduced an intranasal form of "Stimate". This form of Desmopressin acetate is a highly concentrated spray that delivers a therapeutic dose, comparable to the intravenous form, in just two sprays. High-concentrate intranasal Desmopressin acetate significantly simplified the treatment of most Type I vWD patients requiring periodic treatment.

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

TOTAL FACTOR VIII (HEMOPHILIA A + VON WILLEBRAND)

COMPANY	UNITS * (MM)	DOLLARS (MM)	MARKET SHARE	UNITS CHANGE	DOLLARS CHANGE
Aventis Behring **	195	163.800	19.6%	-21.1%	-11.1%
Baxter	775	519.225	62.1%	29.2%	34.7%
American Red Cross	190	70.300	8.4%	72.7%	72.7%
Bayer	49	38.820	4.6%	-54.6%	-52.2%
Wyeth	40	32.000	3.8%	N.A.	N.A.
Alpha Therapeutic	30	12.000	1.4%	400.0%	412.8%
Total	1,279	836.145	100.0%	19.4%	20.5%

* International Units

** Humate P is expressed in Factor VIII units (45 Million units)

6.9) INHIBITORS MARKET

6.9.1) PREVALENCE AND TREATMENT

The incidence of inhibitors among hemophilia patients ranges between 12% and 30% for hemophilia A and 3-10% among hemophilia B patients, depending on the author. In inhibitor patients, the Factor VIII or IX infused to control a bleed are not effective because their system considers them as an antigen, against which antibodies are formed, just as against any other kinds of foreign invaders. The higher level of antibodies formed, the more severe the inhibitor level is. The patients defined as "high responders" develop a large number of antibodies. This number is measured in "Bethesda Unit" (BU). The high responders therefore have an elevated level (above 5 BU per ml of plasma) while the "low responders" have a low "Bethesda Unit" level.

The treatment of the inhibitor patient is difficult because each patient reacts differently to the various treatments and products, and a variety of therapeutic approaches must be tried in these patients in order to control a bleed.

The "low responders" are generally treated with massive doses of Factor VIII or Factor IX in an attempt to overcome the antibodies. Although this treatment is usually effective, the massive dose of Factor VIII may cause the antibody level to go higher, possibly complicating subsequent treatments.

In recent years, "Immune tolerance induction" (IT) has become an increasingly popular treatment of patients with a high level of inhibitors ("high responders"). This procedure consists in infusing the patient with Factor VIII or IX at a high dose (up to 100 IUs per Kg bodyweight per day) in order to "familiarize" his immune system with the existence of Factor VIII or IX until it does not produce antibodies against these coagulation factors anymore. The protocol involves regular infusions for a period ranging from six weeks to twelve months. When immune tolerance is successful, the patient's inhibitor disappears completely or reaches an acceptably low "Bethesda Unit" level, which enables a normal treatment. Once immune tolerance has

been achieved, the patient is said to be "tolerized" (his system can tolerate Factor VIII or IX infusions) or "desensitized" (his system is no longer sensitive to FVIII or FIX infusions). In most patients with inhibitors, the protocol succeeds in six to nine months, and the inhibitor does not return in 75% of patients. Upon completion of immune tolerance, the patients are then put on a "maintenance regimen" involving three FVIII or FIX infusions per week at a lower dose (50 to 60 IUs/Kg) instead of daily infusions, and the protocol becomes similar to a "prophylaxis" regimen prescribed to avoid bleeds in joints. Although immune tolerance induction is initially expensive because it requires large doses of clotting factor for about a year, it results in substantial savings in the long run because the patient no longer needs to undergo expensive inhibitor treatments, he avoids numerous hospitalizations, and his quality of life is significantly improved.

Immune tolerance induction has become popular in recent years due to its favorable long-term effects but it remains less common in the United States than in Europe.

High responder inhibitor patients who are not on immune tolerance are usually treated by means of an activated Prothrombin Complex Concentrates (aPCC), also called "Activated Factor IX Complex", or "Anti Inhibitor Complex Concentrate" (AICC). Baxter's "Feiba VH" and Nabi's "Autoplex T" are the two aPCCs available in the US. The aPCC bypasses the site of action of the Factor VIII antibody, causing the activation of Factor VIII in the coagulation chain. The treatment approach based on aPCC has been the standard approach for the treatment of high responders in the United States. Until a few years ago, non-activated Factor IX Complex, or Prothrombin Complex Concentrate (PCC), such as Bayer's "Konyne 80" (no longer manufactured), Alpha Therapeutic's "Profilnine SD", and Baxter's "Bebulin VH" have been also used. Their share of this market is now insignificant.

In early 1999, Novo Nordisk's "NovoSeven" received FDA approval for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors. Since that time, NovoSeven has received rapid acceptance in the hemophilia community and generated revenues estimated at about

$190 million in 2001. NovoSeven is used for other indications, which may represent 5% to 8% of total sales. Some inhibitor patients who had been treated with an aPCC switched to NovoSeven. In some cases, the treatment of an inhibitor patients involves the combined or subsequent use of NovoSeven and an aPCC.

Another treatment modality consists in using Ipsen's (formerly Speywood) "Hyate:C", a porcine Factor VIII developed in England in the 1980's and available in the US since 1986. This product replaces the missing Factor VIII without being neutralized by antibodies to human Factor VIII. Hyate:C is particularly efficacious in patients who have developed acquired hemophilia (an autoimmune disease) and developed inhibitors to Factor VIII or IX as well. At the beginning of 1998, manufacturing problems occurred at the plant (traces of porceine Parvoviurs B 19) affected some lots of "Hyate:C". Supply became limited, forcing the company to restrict its use to "life of limb saving situations". Sporadic product releases occurred in the following years but the unavailability of Hyate C induced many physicians to use NoviSeven instead. In 2001 sales amounted to an estimated $7 million (from $20 million in 2000). About half of the sales were estimated to be generated by congenital hemophilia patients with inhibitors, and the other half by acquired hemophilia.

Some high level inhibitor patients who do not respond to any of the above products can be treated by means of a "Immunoadsorption system" which has been available for several years in Europe. In 1998, Gambro BCT (formerly Cobe BCT) received an FDA "Humanitarian Device Exemption" for its "Immuno-adsorption system" to be used in the treatment of severe, treatment refractory hemophilia patients with inhibitors. The Excorim Immunoadsorption System comprises a "Spectra" Apheresis System and "Citem 10" extracorporeal plasma handling hardware, linked to a protein A-based double column which selectively removes auto-antibodies against Factor VIII or IX. The device has also been utilized in the treatment of other antibody-mediated immune or autoimmune disorders, including Guillain-Barré syndrome and myasthenia gravis.

Another procedure for patients who did not respond to other therapies is the "Malmø" regimen" involving the administration of intravenous gamma globulin, immuno-suppression and plasma exchange. It aims at replacing the patient's antibody-rich by antibody-poor plasma.

As immune tolerance continues to gain acceptance in the United States, the sales of rFVII:a, aPCC and other products may theoretically go down in the long run while the use of Factor VIII or Factor IX for immune tolerance patients will conversely increase. However, there will always be a need for these products because 25% of the inhibitor patients cannot be "tolerized" and they will need these products throughout their life. Furthermore, these products are used in emergency and surgery for the low level inhibitor patients as well.

6.9.2) MARKET DEVELOPMENTS

In 2001, the "Inhibitors Market" was estimated approximately at $406.9 million when including the value of the Factor VIII and IX concentrate used in immune tolerance, as well as "Hyate:C", and "NovoSeven".

The Inhibitor Market by Major Product and Therapy (US Dollars x MM) - 2000

	Dollars (MM)
Immune Tolerance	$145.5
Profilnine SD	$ 0.6
Feiba VH	$ 55.3
Bebulin VH	$ 0.6
Autoplex T	$ 8.0
NovoSeven	$190.0
Hyate:C	$ 7.0
Total	$406.9

This is based on the assumptions that:

- There are approximately 1,340 hemophilia A or B patients with an inhibitor,
- About 400 of them are undergoing an to IT regimen (370 hemophilia A and 30 hemophilia B patients,
- A dosage of 80 units per day per kilogram bodyweight for 52 weeks,
- An average weight of 20Kg. per patients, because most of them are young children,
- An average price of $74 per unit for Factor VIII and $0.64 for Factor IX. These prices are close, but not equal to the price of rFVIII and rFIX because not all patients use the recombinant products in immune tolerance.

Using these assumptions, the annual consumption of factor VIII is approximately 500,000 international units per hemophilia A patient, and 436,000 units per year per hemophilia B patient. Using these assumptions immune tolerance represents a market of about $145.5 million.

In 2001, the sales of Autoplex T went down by -33.3% in units and -29.8% in dollars over 1999 believed to be attributed to manufacturing problems. From the time of its approval by the FDA in early 1987 until mid-1997, Autoplex T was sold by Baxter. (The original "Autoplex" was approved in 1979). When this company acquired Immuno, the Federal Trade Commission decided that Baxter's monopolistic situation on the inhibitor market required it to sell the distribution rights to Autoplex T to another company, and Nabi was selected. Baxter manufactures Autoplex T for Nabi produces until the company can produce it at its own fractionation plant.

"Feiba VH", Baxter's activated Prothrombin Complex Concentrate (aPCC) is imported from Austria. It received FDA approval at the end of 1982, and was introduced in 1985. "Feiba VH" virus inactivation uses vapor heating. Sales increased slightly in 2001 (+8.3% in units and in dollars).

Over the past few years, the following observations have been recorded:

- A steady progression of the share of NovoSeven,
- A sharp decrease of PCC since 1998
- A gradual decline of Hyate:C,
- A slight progression of immune tolerance, and
- A relative stability, or slight progression of Feiba VH and variations in the market share of Autoplex T, possibly attributed to supply issues.

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

THE INHIBITOR MARKET IN THE UNITED STATES - 2001

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM 2000	
					UNITS	DOLLARS
Nabi	10	0.80	8.0	3.1%	-0.3%	5.3%
Baxter (1)	65	0.85	55.3	21.1%	8.3%	0.0%
Baxter (2)	2	0.29	0.6	0.2%	-25.0%	22.7%
Alpha Therapeutic	2	0.29	0.6	0.2%	0.0%	-1.7%
Ipsen	6	1.24	7.0	2.7%	N.A.	-65.0%
Novo Nordisk (3)	247	0.77	190.0	72.7%	N.A.	20.3%
Total	N.A.		261.4	100.0%	N.A.	N.A.

* International Units/Inhibitor Correction Units/Feiba Units

(1) Feiba VH
(2) Bebulin VH
(2) micrograms

Immune Tolerance Market - 2001

	Number of hemophilia patients	Percent Severe	Percent Inhibitors	Number of patients with an Inhibitor	Percent of patients undergoing Immune Tolerance	Number of patients undergoing Immune Tolerance	Number of international units per year per Patient	Average Factor VIII or IX unit cost	Annual Sales of Factors VIII or IX for IT per patient	Total Units (MM) of Factors VIII or IX for IT per year	Total Dollar Sales (MM) of Factors VIII or IX for IT per year
Hemophilia A	13,300	60%	15%	1,197	31.0%	371	499,200	$0.74	$369,408	185.2	$137.1
Hemophilia B	3,600	50%	8%	144	21.0%	30	436,800	$0.64	$279,552	13.2	$8.5
				1,341		401			Total	N.A.	$145.5

Calculation of the yearly regimen:

IT: 80IUs x 20Kg x 6 times/week x 52 weeks = 499,200

IT: 70IUs x 20Kg x 6 times/week x 52 weeks = 436,800

THE PLASMA FRACTIONS MARKET IN THE UNITED STATES - 2001

ACTIVATED FACTOR IX COMPLEX MARKET

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00 UNITS	CHANGE FROM '00 DOLLARS
Nabi	10	0.80	8.000	3%	-33.3%	-29.8%
Baxter	65	0.81	52.325	21%	8.3%	8.3%
Novo Nordisk	N.A.	0.89	190.000	76%	N.A.	55.1%
Total	N.A.		250.325	100%	N.A.	37.4%

* Inhibitor Correction Units/Feiba Units

Breakdown of Treatments for Inhibitor Patients

Product	Percentage of Patients in the Sample *				
	1998	1999	2000	2001	2002
Feiba VH	37.7	40.3	37.7	39.9	37.6
Immune Tolerance	33.5	30.6	30.3	31.6	25.3
PCC	19.8	17.9	0.2	1.7	0.5
Autoplex T	5.7	9.2	11.1	4.5	6.9
Hyate:C	2.8	1.0	0.3	0.7	0.3
NovoSeven	0.5	1.0	20.4	21.5	29.4
Total	100.0	100.0	100.0	100.0	100.0

* Survey conducted by the MRB

The Inhibitor Care Market in the United States ($ Million) From 1986 to 2001

	aPCC	PCC	F. VIII *	Porcine F.VIII	rFVII:a	Total
1986	17.6	5.0	8.2	-	-	30.8
1987	16.4	5.0	8.2	-	-	29.6
1988	15.0	5.5	6.0	3.0	-	29.5
1989	17.0	3.8	6.5	4.2	-	31.5
1990	17.8	3.0	7.0	6.0	-	33.8
1991	22.1	2.5	7.8	7.5	-	39.9
1992	25.8	2.8	9.2	9.1	-	46.9
1993	31.6	2.6	10.0	14.5	-	58.7
1994	40.2	1.2	12.0	15.0	-	68.4
1995	49.1	0.6	18.0	14.7	-	75.4
1996	45.7	0.5	29.0	12.5	-	87.7
1997	47.8	0.5	42.0	0.5	-	89.8
1998	59.0	6.0	48.0	9.3	-	122.2
1999	61.7	2.6	55.0	20.5	58.0	185.8
2000	59.7	1.5	127.9	20.0	122.5	331.6
2001	63.3	1.2	145.5	7.0	190.0	406.9

* Includes immune tolerance regimen from 1995 onwards.

6.10) OTHER BLEEDING DISORDERS

Other Factor deficiencies affect a comparatively smaller number of patients. For example, it is estimated that less than 200 patients (male & female) suffer from Factor VII deficiency. They are treated with either Proplex T or, increasingly, NovoSeven. The prevalence of Factor XI deficiency affects ten individuals per million people, and they are generally treated with fresh frozen plasma. Factor XIII deficiency (one in a million people) can be treated with Aventis Behring's "Fibrogamin P" on a compassionate basis, as this product, made in Germany, in not approved in the United States.

7) ALPHA-ONE ANTITRYPSIN MARKET

7.1) MARKET DEVELOPMENTS

In 2001, the sales of Bayer's "Prolastin" (Alpha-1 Proteinase Inhibitor) were estimated at $89.2 million, a 17.1% decline from 2000, both in units and dollars. The decline was attributed for the major part to manufacturing difficulties.

The "Alpha One Foundation" provides support and advice to patients with congenital Alpha-One Antitrypsin deficiency, the number of which is estimated at about 5,000 in the U.S.

Until the end of 1999, Prolastin was primarily distributed through home care companies, in particular Gentiva and Caremark. In order to streamline the distribution in the product which was in short supply in the late 1990's and to facilitate access to the product, Bayer initiated "Bayer Direct", a direct distribution program in late 1999. By enabling patients to order the product directly from the manufacturer, this program bypassed the home care companies, distributors or brokers, and avoided stockpiling.

Alpha-1 Proteinase Inhibitor was introduced by Bayer in 1988. It is prepared from Fraction IV-1 paste. The process yields about 0.250 grams per liter of plasma. The product is indicated for the treatment of congenital Alpha-1 Antitrypsin deficiency with early signs of emphysema, and received Orphan Drug status.

Patients with congenital emphysema need weekly infusion of Alpha One Antitrypsin for life at a dose of 60 mg per Kilogram bodyweight per week. As new patients were identified every year since 1988, Bayer experienced increasing difficulties to meet the demand, leading to a shortage in 1997/98. Although the company took the necessary measures to alleviate the shortage, the supply has been tight in recent years.

The Alpha One Antitrypsin Market from 1988 to 2001

	$ Million	% Change
1988	5.0	-
1989	8.8	+76%
1990	15.2	+73%
1991	20.6	+36%
1992	29.4	+43%
1993	38.5	+31%
1994	44.4	+ 5%
1995	46.4	+ 4%
1996	52.2	+ 4%
1997	54.9	+ 5%
1998	60.3	+ 16%
1999	54.4	- 10%
2000	107.6	+ 98%
2001	89.2	- 17%

The end of Prolastin's orphan drug status and the shortage of the late 1990's encouraged several companies to seek a share of this market, and to develop new products to treat congenital emphysema.

7.2) COMPETITIVE PRODUCTS IN DEVELOPMENT

Alpha Therapeutic

In 2001 Alpha Therapeutic reported that it planned to file a Biological License Application (BLA) with the FDA for the approval of a new plasma-derived alpha-1 antitrypsin product for the treatment of hereditary emphysema. Approval is expected sometime in later 2002 or early 2003.

Aventis Behring/Inhale Therapeutics

In 1999 Aventis Behring and "Inhale Therapeutics" began a clinical trial of a spray formulation of a new plasma-based alpha-1 proteinase inhibitor. The FDA gave Orphan Drug designation to this agent. Aventis Behring produces the active product from source plasma, which is then turned by Inhale into a dry powder for inhalation administration. Aventis Behring has built a new manufacturing facility to manufacture

this new product which will be sold in Europe and elsewhere, including the US, once approved by the FDA.

Bayer/PPL Therapeutics

In 2000, Bayer and the Scottish biotechnology firm "PPL Therapeutics" signed an agreement for the development of Alpha-1 Antitrypsin from sheep milk. Bayer made a $15 million equity investment and agreed to fund the clinical trials for the treatment of congenital emphysema and cystic fibrosis. The product, which is formulated as an aerosol, has completed phase II clinical trial, and phase III is expected to begin shortly. Approval is not expected before 2007

Baxter/Arriva

In 2000, Baxter and "Arriva" (formerly called AlphaOne Pharmaceuticals) signed an agreement to jointly develop an inhaled, recombinant alpha-1 antitrypsin indicated for the treatment of congenital emphysema and possibly other disease conditions in the future (asthma, cystic fibrosis and chronic obstructive pulmonary disease (COPD). Arriva's product is genetically engineered in yeast cells, using a patent licensed from ZymoGenetics. The agreement gave Baxter exclusive worldwide marketing and distribution rights for Arriva's recombinant alpha-1 antitrypsin.

Separately, Arriva has a joint venture with the Canadian firm "ProMetic Life Sciences" for the use of its recombinant alpha-1 antitrypsin to treat various dermatologic diseases.

8) ANTITHROMBIN III MARKET

In 2001, the Antithrombin III (ATIII) market amounted to $2.7 million, a 45.5% decrease from 2000 in value and volume. Bayer was the sole supplier in the United States. The product is losing acceptance in the medical community, due to controversial efficacy. Furthermore, the manufacturer does not promote it aggressively

AT III deficiency occurs as a consequence of trauma, shock, sepsis or complicated pregnancy. It is also a rare inherited disorder, affecting some 3,000 individuals in the United States. AT III replacement therapy normalizes the plasma antithrombin level, restores the balance of the coagulation system, and helps avoid the catastrophic consequences of uncontrolled coagulation, such as Disseminated Intravascular Coagulation (DIC). The occurrence of DIC activates the coagulation cascade, which massively consumes the body's supply of AT III. In a DIC state, the patient's body is unable to generate enough AT III, and its level falls dramatically, often leading to a fatal outcome. AT III Replacement therapy stabilizes the coagulation system, buying time to treat the underlying cause. The first Antithrombin concentrate, "Atenativ", made by Biovitrum was approved by the FDA in early 1990, and distributed by Baxter in the U.S. Baxter ceased selling Atenativ some three years ago, leaving the entire market to Bayer.

Bayer's "Thrombate III" was approved in December 1991 and launched in early 1992. It is indicated for the treatment of patients with hereditary AT-III deficiency in resulting from surgical or obstetrical procedures or thromboembolism. A few years ago, Aventis Behring undertook a large international, multicenter clinical trial of its "Kybernin P" (the "Kybersept" trial) in an indication of severe sepsis and septic schock. As the results of the trial were disappointing, Aventis Behring did not pursue the U.S. licensure of its AT III product.

The development of the AT III market in the U.S. is limited by the restricted product indications, and cost containment, as Antithrombin III is subjected to PHS pricing, as the clotting factors.

The Antithrombin III Market in the United States ($ Million) from 1993 to 2001

	1993	1995	1997	1998	1999	2000	2001
Baxter/Kabi	1.5	3.0	0.2	-	-	-	-
Bayer	2.0	6.1	8.1	12.0	9.4	11.0	2.7
Total	3.5	9.1	8.3	12.0	9.4	11.0	2.7

In 1996, Genzyme Transgenics submitted an IND to the FDA to begin the clinical trials of an ATIII produced from the milk of transgenic goats. The initial indication sought was coronary artery bypass surgery, but the results were disappointing. The company then decided to seek the congenital AT III deficiency indication only with a view to demonstrate the approvability of a drug made from the milk of transgenic animals. The study is now conducted in Europe only.

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ANTITHROMBIN III

COMPANY	UNITS * (MM)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00	
					UNITS	DOLLARS
Bayer	6.0	0.45	2.700	100%		
Total	6.0		2.700	100%	-45.5%	-45.5%

* International Units

ALPHA 1 PROTEINASE INHIBITOR

COMPANY	UNITS * (000)	A.S.P. $	DOLLARS (MM)	SHARE %	CHANGE FROM '00	
					UNITS	DOLLARS
Bayer	435	205.0	89.175	100%		
Total	435	205.0	89.175	100%	-17.1%	-17.1%

* 500 IU vials

FIBRIN GLUE

COMPANY	UNITS * (000)	A.S.P. $	DOLLARS (MM)	MARKET SHARE	CHANGE FROM '00	
					UNITS	DOLLARS
Baxter	340	92.0	31.280	73%	25.9%	8.3%
Haemacure	120	97.0	11.640	27%	0.8%	-6.8%
Total	460	93.3	42.920	100%	18.3%	3.7%

* 1 mL equivalent

9) FIBRIN SEALANT MARKET

9.1) MARKET DEVELOPMENTS

In 2001, the Fibrin Sealant market amounted to $42.9 million, with approximately 460 liters of product sold. This represented an increase of 18.3% in volume but only +3.7% in dollars, as the average price dropped from $106.4 per mL in 2000 to an average of $93.3 per mL in 2001.

Baxter continued to dominate the market with a 72.9% market share although the company lost 15 percentage points to Haemacure, which increased its share to 27.1% of the market in 2001. Haemacure uses a 12-person sales force while Baxter hired some 16 sales representatives, and uses part time sales representatives as well.

The FDA approved "Tisseel VH", Baxter's tissue sealant in May 1998. It is vapor heated and comprises fibrinogen, human thrombin and aprotinin. As Baxter acquired Immuno in 1997, the Federal Trade Commission (FTC) ruled that the company would have a monopolistic advantage as it would be the sole supplier of fibrin sealant in the U.S. Therefore, the FTC compelled Baxter to license the right to Tisseel to another distributor. the Canadian company "Haemacure" obtain this right and began to sell its own version of the product under the name "Hemaseel APR" in the U.S. at the same time as Baxter which retains its rights on "Tisseel" outside of the United States. The product is manufactured by Baxter in Vienna, Austria from U.S. plasma.

As the FTC ruling stipulated that Haemacure would have to use an alternate manufacturer of "Hemaseel APR" than Baxter, Haemacure concluded a manufacturing agreement with Bio Products Laboratory (BPL) in 2000 to produce "Hemaseel APR", and possibly its new "Hemaseel HMN", currently in phase III clinical trial.

In 2000, Baxter received FDA approval for its "Tissomat", an application device and spray set for the application of Tisseel. Tissomat facilitates the sealing of large wound surfaces by delivering a uniform layer of fibrin glue that can cover a surface area

approximately 12 times greater than the currently used "Duploject" applicator.

For its part, Haemacure received FDA clearance to commercialize its own proprietary aerosol delivery device called "HemaMyst".

In 2002, Haemacure re-negotiated a development and commercialization agreement for its proprietary "Hemaseel HMN" fibrin sealant product with ZLB Bioplasma AG in Bern, a subsidiary of CSL Ltd. (Australia). Haemacure now assumes responsibility for the clinical testing, registration and manufacture of Hemaseel HMN, which has already been evaluated, in several clinical trials over the past three years. In return for the transfer of remaining obligations under previous agreements and a 3% royalty on net revenues of the initial Hemaseel HMN product over a 10-year period, ZLB Bioplasma agreed to provide the following to Haemacure:

- A cash payment of Can $12.7 million ($8.1 million) in three specified installments,
- Manufacturing/filling equipment suitable for making Hemaseel HMN,
- ZLB Bioplasma documents and a perpetual license to ZLB Bioplasma proprietary technology related to the Hemaseel HMN project, as well as technical assistance for up to three years,
- Funding of up to Can $7.2 million ($4.6 million) upon achieving certain Hemaseel HMN development milestones, and
- Up to 50,000 liters of human plasma.

The original agreement for Hemaseel HMN development was between Haemacure and the ZLB Central Laboratory of the Swiss Red Cross, which was purchased in September 2000 by the Australian plasma fractionator CSL. The restructured deal gives Haemacure exclusive worldwide manufacturing and marketing rights to Hemaseel HMN, a second-generation product. Hemaseel HMN will be produced either by BPL, or by a new facility to be built in Montreal. The company projects Canadian, European and U.S. marketing approvals for Hemaseel HMN in 2005.

Among other potential competitors, Aventis Behring has been expected to introduce "Beriplast P". Alpha Therapeutic is reported to be developing a fibrin sealant, and Omrix Biopharmaceuticals (Brussels, Belgium) is reportedly still pursuing its clinical trial in the U.S. The American Red Cross has ended all activities regarding the development of a proprietary fibrin sealant. Other fibrin sealants, non plasma-based or made from autologous human plasma, have been developed or commercialized by:

9.2) COMPETITIVE PRODUCTS IN DEVELOPMENT

PPL Therapeutics

PPL Therapeutics plans to introduce "Fibrin 1", a single-component fibrin sealant technology licensed from Bristol Myers Squibb. It is easier to manufacture than the conventional three-component fibrin sealants (fibrinogen, thrombin, Factor XIII), it reportedly offers comparable hemostasis and tissue sealing, and seems to reduce the risk of intraabdominal adhesions in animal models. "Smith and Nephew" originally partnered with PPL to develop a transgenic fibrinogen version for certain orthopedic and wound care indications, but is now developing the plasma-based version. Meanwhile, PPL is seeking additional marketing partners. While the plasma-based product offers a faster path to licensure, PPL plans to develop a follow-on "Fibrin 1" product using transgenic fibrinogen as the primary raw material.

Fusion Medical

Approved for marketing in December 1999, "FloSeal" is a combination of collagen-derived particles and topical bovine thrombin, which is promoted to achieve hemostasis even on wet, actively bleeding tissue. Sales in the fourth quarter of 2001 amounted to $4.5 million. Fusion has several other related products in various stages of development and clinical testing for use as hemostatic sealants and for other potential uses. In early 2002, Baxter Bioscience acquired Fusion Medical for $157 million.

Cryolife

Cryolife has developed and commerializes "Bioglue". Classified as a device, this glutaraldehyde-crosslinked bovine albumin product has been available in the United States under an FDA-approved Humanitarian Device Exemption (HDE) since 1999, for adjunctive use in the repair of acute thoracic aortic dissection, a life-threatening condition. BioGlue is approved for cardiac, vascular and pulmonary repairs in 36 countries outside the U.S. Abdominal aortic aneurysm repairs, endarterectomy surgeries, sealing of suture lines, aortic dissections and aortic root replacements, gluing/sealing of organs, dural sealing, A-V access device sealing, femoral popliteal bypasses, coronary artery anastomoses are some of BioGlue's clinical applications. Worldwide sales are about $4.9 million per year.

Cohesion Technologies

Cohesion Technologies developed "CoStasis" a collagen/thrombin suspension to be mixed with the patient's own plasma when applied to the bleeding site. In 2000, the FDA approved CoStasis as a surgical hemostat. It is distributed by U.S. Surgical.

"CoSeal" Cohesion's non plasma-based proprietary surgical sealant was approved by the FDA in December 2001. It is indicated in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing the areas of leakage. Once dispensed from the applicator, CoSeal is self-activating and polymerizes in seconds to form a flexible hydrogel seal

ThermoGenesis

In 1999, ThermoGenesis received FDA approval for its "CryoSeal AHF System" device, which isolates cryoprecipitate from plasma rapidly. It is a "computer-controlled, portable system for producing fibrinogen-rich AHF from a unit of donor plasma in less than sixty minutes." In 2001, the company completed the clinical trials of a device specifically designed to produce autologous fibrin glue, the "CryoSeal AHF System".

9.3) MEDICAL INDICATIONS OF FIBRIN SEALANTS

Fibrin sealants have been used in the United States for many years. While they cannot replace sutures and staples in surgery requiring a strong tensile capability, they have several advantages over sutures:

- Rapid clot formation,
- Reduced inflammation because fibrin glue is less invasive than sutures and staples,
- Absence of scar,
- Ability to close areas that are difficult to close with sutures,
- Reduced loss of blood or other body fluids,
- Higher accuracy in the dosage. Dosage consistency (advantage of the commercial concentrates over blood bank glue),
- Occasionally, the patient's blood has a low fibrinogen level, and the autologous blood bank glue does not work.

For a long time, many hospitals across the country have prepared fibrin adhesives from autologous or allogeneic blood in their coagulation laboratory for surgical purposes. Since the cryoprecipitate used in the formulation is not virus inactivated, its safety is questionable. The advantages of the commercial fibrin sealants over "home-brewed" fibrin glues prepared from bovine thrombin and donor human plasma include:

- A highly controlled manufacturing process;
- Consistent potency from batch to batch;
- Multiple processes for viral inactivation of blood-borne pathogens.

All the fibrin sealants comprise fibrinogen, thrombin, and calcium chloride. Some include Factor XIII, and others, such as the Baxter product, contain aprotinin.

10) DISTRIBUTION OF PLASMA PRODUCTS

10.1) PRIMARY AND SECONDARY MARKET

Plasma products are traditionally distributed by the manufacturers to wholesalers, which dispatch them to hospitals. The market may be divided into two main segments:

1) The "primary market" involves the manufacturers and hospitals, themselves organized in Group Purchase Organizations (GPOs). Purchasing contracts between the manufacturers and GPOs are generally negotiated every year, often toward mid-year. About two thirds of the production of plasma products is purchased by ten to twelve large buying organizations.

2) The "secondary market", also called "spot market" is made up of a dozen of "distributors" or "dealers" of various scopes and sizes. Some of them distributes pharmaceutical drugs as well as plasma products, others only deal in plasma derivatives, offering generally the complete portfolio from several fractionators.

To a large extent, clotting factors are distributed outside the above-mentioned markets, as they are mainly channeled from the manufacturers to the patients through home care companies. These companies move an estimated 60% to 65%% of the coagulation products, both plasma-derived and recombinant.

The distinction between a wholesaler and a distributor is somewhat blurred, as some large distributors (such as FFF Enterprises) may be considered as a wholesaler, given the volume of product purchased and the volume of their operations. Dealers and distributors offer their services and products to hospitals and clinics but they differentiate themselves from the wholesalers and from the "primary market" by the fact that they generally do not have any long term contracts with their hospital clients. By product line and type of distribution channel, the market is broken down as follows:

Polyvalent Intravenous Immune Globulin (IGIV)

Type of Customer	Percent of Market
Hospitals (through GPOs)	75%
Home care Companies	15%
Infusion Suites & Physicians offices	5%
Distributors	5%

Albumin

Type of Customer	Percent of Market
Hospitals (through GPOs)	59%
Home care companies	2%
Distributors	39%

Coagulation Factor Concentrates

Type of Customer	Percent of Market
Hospitals & Treatment Centers	30%
Home Care Companies	65%
Distributors	5%

10.1.1) GROUP PURCHASE ORGANIZATIONS (GPOS)

Group Purchase Organizations are umbrella organizations whose members are healthcare providers, including hospitals. These providers benefit from economy of scale by sharing buying power, marketing efforts and name identification.

The largest GPOs work with three to four selected wholesalers but hospitals and manufacturers are increasingly being offered more favorable terms when they use a single channel of distribution, which limits the manufacturer's distribution options. The GPOs have undergone a series of mergers and acquisitions, and with respect to biological products, some of the main GPOs include, in descending order of IVIG and albumin business (rough estimates):

- Premier Purchasing Partners is making an estimated $275 million worth of IVIG and albumin business. It is serviced by FFF Enterprises, under a five year contract, which comes for renewal in mid 2003. Premier has about 1,500 member hospitals.

- Novation is the merger of the "University Hospital Consortium" (UHC) and the "Voluntary hospitals of America" (VHA). This group is the second largest in terms of plasma products business with an estimated $250 million worth of IVIG and albumin purchases per year. It is serviced by FFF Enterprises, NSS, and ASD among others.

- Columbia/HCA Healthcare is making an estimated $75 million worth of IVIG and albumin business. It operates about 300 hospitals, as well as a number of home health care agencies.

- Consorta is making an estimated $50 million worth of IVIG and albumin business every year. It is the hospital group formed by the hospitals of the "Daughters and Sisters of Mary".

- Cardinal/NSS/Owen Health Care is making an estimated $20 to $30 million worth of IVIG and albumin business.

- Amerinet is making an estimated $30 million worth of IVIG and albumin business.

- Tenet Healthcare (now "Broadlane") is making an estimated $30 million worth of IVIG and albumin business. Tenet has about 1,400 member hospitals.

- MHA, formerly called "MedEcon Services Inc." has joined NSS.

- InSource and HSCA have joined forces to form "Medassets/HSCA".

- The Veterans' Health Administration does not buy as much IVIG and albumin as the above groups.

Some Health Maintenance Organizations, such as "Kaiser Permanente" also operate as Groups purchase organizations with respect to plasma products.

10.1.2) WHOLESALERS

In recent years, a consolidation of the pharmaceutical wholesalers sector occurred through the purchase of regional or local distributors.

The wholesalers execute the contracts signed between manufacturers and hospitals or group purchase organizations. Their services are remunerated with a fee ranging from two to five percent of the value of the products sold. They are not involved in the pricing negotiation between manufacturers and GPOs or individual hospitals.

The majority of wholesalers and most large manufacturers belong to the National Wholesale Druggists' Association (NWDA). NWDA member wholesale drug corporations operate about 230 distribution centers in the United States. With respect to plasma products, the main wholesalers are:

- Bergen Brunswig Drug Company is the largest supplier of pharmaceuticals to the managed care market and the second largest wholesaler to the retail pharmacy market. In 1994, Bergen Brunswig established a subsidiary dedicated to plasma products called "Alternate Site Distributors" (ASD) based in Dallas, Texas. This organization set up an internet purchasing program called "Pharmabid" which is used primarily for short-dated products.

- McKesson Drug Company: With its 45 drug distribution centers and 6,000 employees, McKesson serves more than 122,000 products for 17,000 chain and independent drug stores and 3,000 hospitals and health care dealers.

- Cardinal Health has 35 regional distribution centers nationwide. Its subsidiary called "National Specialty Services" (NSS) is dedicated to the plasma products market

- AmeriSource Health Corporation operates 16 full-service drug wholesale distribution facilities and one specialty products distribution facility. The company serves 18,000 customers in 37 states, with a stock of 100,000 items purchased from over 800 suppliers.

Other regional distributors include Morris Dickson (Louisiana), Alapharma, (Alabama), etc.

10.1.3) DEALERS AND DISTRIBUTORS

"Dealers" or "distributors" purchase products directly from the manufacturers, or occasionally from other distributors, especially in case of shortages. They serve hospitals on an "ad hoc" basis, supplying the "spot" market. Their prices are generally higher than the GPO prices because they cannot predict their sales in advance. However, their prices may be lower if there is glut, and some hospitals buy on the spot market even if they belong to a Group Purchase Organization (GPO). The largest dealers of plasma products are, in no particular order:

- Chapin Medical
- FFF Enterprises
- CT International
- ActSys Medical Inc.
- Williams Medical
- Davis Enterprises
- Paragon Scientific Corp.
- ASD (Bergen Brunswig)
- IDP, Inc.
- Blood Diagnostics
- National Specialty Services ***
- Florida Infusion
- National Hospital Specialties
- Alpine Biologics
- Atlantic Business Organization
- Health Coalition
- J-Mark Enterprises
- BioCare *
- Western Medical Supplies **
- Davis Enterprises
- Biomed Plus
- Genesis Bio-Pharmaceuticals

* Subsidiary of United Blood Services
** Division of SeraCare
*** Subsidiary of Cardinal Health

Since almost each one of these companies is privately owned, their sales are not disclosed. Industry information suggests that the largest ones are, in declining order of sales of plasma products only, in 2001:

First tier
- FFF Enterprises (estimated at $350 million)
- National Specialty Services (NSS, $260 million?)
- ASD ($250-$260 million?)
- Health Coalition ($450 million?)
- Alpine Biologics, before it lost the ZLB franchise, ($250 million?)

Second tier
- Biomed Plus ($100 to $150 million?)
- Blood Diagnostics ($75-$100 million?)
- National Hospital Specialties (NHS, ($30-50 million?)
- Genesis Bio-Pharmaceuticals ($50 million?)
- ActSys Medical
- Biocare
- Atlantic Business Organization ($10-$20 million?)

Third tier
- Chapin Medical,
- Paragon Scientific Corp
- CT International
- Williams Medical
- Western Medical Supplies
- Davis Enterprises

The activities of the companies in the "first tier" may be assimilated to a wholesalers' role, as they often operate as the distribution branch of some GPOs. Conversely, some of those listed in the third tier have a sporadic activity in the plasma business, and/or are reported to be in a difficult financial situation, or in transition (e.g. from the plasma business to other types of drugs).

In time of product shortage, the role of distributors is crucial, as they fill urgent procurement gaps, and can in fact intervene quickly in emergency situations. The 1998 IGIV shortage underlined their role

although it also generated the negative image created by a minority of dealers who allegedly stockpiled product and engaged in speculative operations.

DEALERS AND DISTRIBUTORS: ADDRESS, PHONE & FAX

Chapin Medical Company
P.O. Box 699
Corona, CA 91718
Phone: (909) 735-5300
(800) 221 7180
Fax: (909) 735-6117

FFF Enterprises
41093 County Center Drive
Temecula, CA 92591
Phone: 800-843-7477
Fax: (800) 418-4333
(909) 506-6842

Genesis Bio-Pharmaceuticals
9 Brick Court
Tenafly, NJ 07670
Phone: (201) 488-0998

National Hospital Specialties
65 Commerce Way
Hackensack, NJ 07601
Phone: (201) 488-1174
(800) 344-6087
Fax: (201) 488-0983

CT International
4349 Santa Fe Road
San Luis Obispo, CA 93401
Phone: (805) 544-5572
(800) 755-7575
Fax: (805) 544-5796

Alpine Biologics Inc.
33 Kings Highway, Suite One
Orangeburg, NY 10962
Phone: (914) 680-9426
(800) 442-5746
Fax: (914) 680-9471

ActSys Medical
31336 Via Colinas, Suite 101
Westlake Village, CA 91362
Phone: (800) 808-9094
Fax: (818) 707-9094

National Specialty Services, Inc.
556 Metroplex Drive
Nashville, TN 37211
Phone: (800) 879-5569
Fax: (615) 333-4306

Atlantic Business Organizations (ABO)
6046 Cornerstone Court West
Suite 206
San Diego, CA 92121
Phone: (619) 453-9516
Fax: (619) 453-2133

Williams Medical Company
1150 South Las Brisas Place
Placentia, CA 92870
Phone: (800) 252-8646
Fax: (714) 961-8914

Health Coalition
4906 SW 72nd Avenue
Miami, FL 33155
Phone: (305) 662-2988
Fax: (305) 667-5389

Davis Enterprises
521 South Third Street
Phoenix, AZ 85020
Phone: (800) 800-2987
Fax: (602) 253-6821

J-Mark Enterprises
20405 State Hwy. 249, Ste. 200
Houston, TX 77070
Phone: (281) 376-0544
Fax: (281) 251-2025

Paragon Scientific Corporation
301 Lavaca Street
Austin, TX 78701
Phone: (512) 476-3330
Fax: (512) 476-3303

BioCare
6210 E. Oak Street
Scottsdale, AZ 85252
Phone: (480) 675-7101
(800) 304-3064
Fax: (480) 675-7104

ASD
4006 Beltline Road
Suite 200
Addison, TX 75001
Phone: (800) 837-5403
Fax: (972) 490 5551

Bio Med Plus
7001 N. Waterway Drive
Suite 103
Miami, FL 33155
Phone: (305) 666-0389
Fax: (305) 666 8071

Western State Plasma
1935 Avenida del Oro
Suite F
Oceanside, CA 92056
Phone: (760) 806-8922
Fax: (760) 806-8933

Specialty Blood Products, Inc.
1101 S. Rogers Circle
Boca Raton, FL 33487
Phone: (561) 989-8886
Fax: (561) 989-8131

IDP, Inc.
c/o ABA Trading
6560 West Rogers Circle
Suite 27
Boca Raton, FL 33487
Phone: (561) 995-6990

10.1.4) HOME CARE

Home health care has been growing rapidly in recent years. In the field of hemophilia, a number of small home care companies, some of which were created by former employees of the larger ones, have been created. Several companies involved in hemophilia care employ hemophiliacs who know the needs of patients first hand. As they are close to the patients, they have a competitive edge over the large organizations with. Some home care companies are an extension of hospital outpatient services, and enjoy the logistical support and possibly financial backing of the hospital.

Many home care companies have been financially successful in the recent past by generating revenues from the difference between the Average Wholesale Price (AWP) and the acquisition price they paid the manufacturers for clotting factors. While the expenses for drugs are not a high percentage of home health care in a number of disease conditions, it is by far the most expensive budget item in home

hemophilia care. The differential between the AWP and the acquisition price of clotting factors has been denounced as some sort of an "excessive profit" by various groups, including those advocating PHS pricing who benefited themselves from the situation. The home care companies, however, underlined that the services rendered to the hemophilia patients, besides and beyond the provision of coagulation factor concentrates, were largely absorbed by the difference between the AWP and the acquisition price of clotting factors. Such services include drug for AIDS or hepatitis C treatment for those who suffer from these diseases, nurses visit, psychological support, physical therapy, ancillary products (helmet, pillows, etc), communications devices, support to summer camps training and community activities, and many other services or products.

The main home care companies involved in the home treatment of hemophilia patients are "Caremark Therapeutic Services", "Gentiva Health Services", and "Hemophilia Health Services" (Memphis, TN), Other companies of a lesser size include "American Hemophilia Federation", (AHF, Enfield, CT), "Hemophilia Resources of America" (New Jersey), "NuFactor" (a division of FFF Enterprises), "Chronimed", "Apria," etc. "AlphaNet" (Florida) specializes in the care of AAT-deficient patients. In 1997, HHS acquired "Nova Factor" (Knoxville, TN), thus becoming the third largest hemophilia home care company after Caremark and Gentiva. In 2001, Hemophilia Health Services (HHS) and its recent acquisitions "Nova Factor" and "Sunrise Health Management" were acquired by "Accredo Health". Later in the year, Accredo Health acquired "Biopartners in Care".

In early 2002, "Gentiva Health Services" announced that its Specialty Pharmaceutical Services – which serves the hemophilia and IVIG communities – would also be acquired by Accredo Health. To better streamline its home care activities, Accredo split the hemophilia and the IVIG sectors: Sunrise Health Management, "Pharmacare Resources of America", and a new company to be created as a result of the acquisition of Gentiva's IVIG business would focus on IVIG therapy while the others will continue serving the hemophilia community.

In early 2002, "Curative Health Services" acquired "e-BioCare", "Hemophilia Access" and Apex Therapeutics Care. Furthermore, "Priority Health Care" acquired the largest home care company in Florida, "Hemophilia of the Sunshine States".

11) PROFILES OF THE MAJOR FRACTIONATORS

11.1) ALPHA THERAPEUTIC

2410 Lillyvale Avenue
Los Angeles, CA 90032
Phone: (800) 421-0008
Fax: (323) 441-7968
Web: www.alphatherapeutic.com

After nearly two years of sporadic production interruptions caused by investments and enhancements required to meet GMP standards, Alpha Therapeutic resumed full production in early August 2001. As a result, 2001 sales in the United States jumped 226% from $39.9 in 2000 to $130.2 million. This included only finished products, as Alpha sold bulk products to other manufacturers.

In early 1998, the company entered into a "Consent Decree" with the FDA, which required certain enhancements to manufacturing controls, employee training and quality assurance. As a result, the company undertook in a major overhaul and expansion of its fractionation facility, adding 80,000 square feet to the existing plant.

In May 2001, signed a co-marketing agreement with the American Red Cross, under which Alpha's sales force would promote Red Cross' "Monarc-M" (Factor VIII concentrate). This agreement ended in early 2002, as the strong demand for the product no longer required Alpha's sales support.

Under an agreement with the American Red Cross, Alpha processed partially finished plasma collected by the American Red Cross into Factor IX that was distributed by the American Red Cross under the Alpha's label. This agreement has now been terminated.

Late in 2001, Alpha announced that it planned to file a Biological License Application (BLA) with the FDA for approval of an alpha-1 antitrypsin product for the treatment of hereditary emphysema.

In May 2002, Mitsubishi Pharma announced that it Alpha Therapeutic was offered for sales. Besides the fractionation plant, the business includes 42 plasma collection centers, a testing laboratory in Memphis, and Alpha Therapeutic Services, a home infusion therapy unit.

11.1.1) HISTORICAL DEVELOPMENT

In 1967, Abbott Laboratories acquired the Courtland Laboratories, then sold its plasma operations to the Green Cross Corporation of Japan for $22 million in 1978. The Laboratory was renamed "Alpha Therapeutic". In 1982, Alpha acquired 50% of Grifols Laboratories of Spain.

In 1988, Alpha's fractionation plant in Los Angeles had an initial throughput of about 1.1 million liters of plasma per year. The capacity was increased to 1.8 million liters in 1986. In 1987, Alpha further increased its capacity and added a new purification process, which also increased the yields. In 1992, some $15 million was invested into the modernization of the fractionation plant. In 1994, the company spent $38 million to further upgrade its facility, which now has an estimated fractionation capacity of two million liters of plasma per year.

In 1998, the Green Cross Corporation, Alpha's parent company, merged with Yoshitomi, which changed its name to "Welfide" in early 2000. In 2001, Welfide was acquired by Mitsubishi Pharma, and the latter's administrative staff was relocated from Osaka to Tokyo.

In 1999, Welfide decided to divest its 50% interest in the Grifols Group.

11.1.2) U.S. SALES RESULTS

In 2001, the breakdown by product of Alpha's sales of finished products was:

Product	*Dollars (MM)*	*Percent*
IGIV	76.5	58.7%
Fraction V	22.9	17.6%
Factor VIII	2.3	9.2%
Factor IX	18.2	14.0%
Factor IX Complex	0.6	0.4%
Total	130.2	100.0%

The company's last ten year sales history is shown below:

Alpha Therapeutic Sales from 1987 to 2001 ($Million)

	$MM	*Change*
1987	27.3	+34%
1989	47.0	+21%
1991	93.9	+36%
1993	137.1	+23%
1995	187.3	+12%
1996	219.5	+17%
1997	236.8	+ 8%
1998	242.8	+ 3%
1999	86.5	- 64%
2000	39.9	- 53%
2001	130.2	+ 225.9%

In 2001, the sales force comprised some 20 sales representatives including four Regional Managers and one National Director of Sales for plasma products.

All the Alpha operations, both domestic and international are concentrated in Los Angeles.

Sales by Alpha to its parent company, Mitsubishi (formerly Welfide, Yoshitomi, and previously, the Green Cross Corporation) accounted for over 90% of Alpha's revenues in the early 1980's. As Alpha diversified its markets, this percentage declined gradually over the years, and now represent a small share of the company's revenues.

11.1.3) PRODUCT LINE

Polyvalent Intravenous Immune Globulin (IGIV)

"Venoglobulin S", a third generation IVIG liquid Intravenous Immune Globulin Solvent Detergent-treated, 5% and 10% solution. "Venoglobulin-S 10% Solution" received FDA approval in 1995. This liquid solvent-detergent treated IVIG preparation was formulated at twice the concentration of Venoglobulin-S 5% launched in 1991. In 1997, Venoglobulin-S was approved by the FDA for the additional indication of Kawasaki Disease.

"Venoglobulin-S10% Solution" is available in 5.0 grams (50 ml vial), 10.0 grams (100 ml vial) and 20 grams (200 ml vial) sizes. Storage at room temperature of the 10% solution was approved by the FDA in 1998.

Albumin and Plasma Protein Fraction (Fraction V)

"Albutein": Human Serum Albumin
"Plasmatein" Plasma Protein Fraction. Still licensed, no longer manufactured.

Coagulation Factor Concentrates

"Alphanate": Factor VIII Concentrate Solvent Detergent and heat-treated. It was approved by the FDA in August 1994. Its von Willebrand molecule portion is attached to factor VIII:C. allowing the treatment of vW disease. Alpha's former Factor VIII concentrate "Profilate OSD" has been phased out in favor of Alphanate. Alphanate received approval for the treatment of von Willebrand's disease in the UK in November 2001.

"AlphaNine SD": Factor IX Concentrate, Solvent Detergent-treated, was the first "pure" Factor IX on the U.S. market. It was introduced in 1991 in the U.S. at the initial list price of 90¢ per unit. A new formulation of AlphaNine SD was licensed in 1992. Alpha also offers "Profilnine SD", a Prothrombin Complex Concentrate, Solvent Detergent-treated.

Alpha also manufactures a Fibrinogen concentrate, the license of which is still pending.

In 1996, Welfide (now Mitsubishi) established a subsidiary to produce recombinant albumin. The company, called "Bipha", built a plant in Hokkaido in 1997 to produce large quantities of recombinant albumin. The facility was reported to have a production capacity of three million 50 ml vials of 25% albumin per year. The product was submitted for Japanese marketing authorization in 1997 and it has not been approved as of mid-2002.

Initially, Welfide intended to offer the product for non-therapeutic applications (biotechnology and diagnostic applications) but this decision was reconsidered in the light of the low price of albumin in this sub-market in Japan, as opposed to the high price that can be obtained in the therapeutic albumin market.

11.2) AMERICAN RED CROSS

1616 Fort Myer Drive
17th Floor
Arlington, VA 22209
Phone (703) 312-5600
Fax: (703) 312-5772
Web: www.usa.redcross.org

In 2001, the sales of plasma derivatives by the American Red Cross (ARC) Biomedical Services were estimated at $378.8 million, a 30% increase from 2000 ($291.3 million).

The increase was mainly attributed by strong sales of "Polygam SD" IVIG (+66.7% from 2000), and of "Monarc M", Factor VIII concentrate (+72.7%). Monarc M's success was caused largely by the conversion of many hemophilia patients who were unable to obtain Kogenate FS or another recombinant product during the shortage of these products. By mid-2002, as Bayer was able to release more Kogenate, the sales of Monarc began to abate. Albumin sales declined by 11.6% in volume and 17.3% in dollars.

This did not include the revenues generated by "PLAS+SD", a solvent detergent-treated plasma manufactured on contract by V.I. technologies since 1998. In April 2002, the ARC announced that it would discontinue supplying PLAS+SD once current inventories were depleted because "the manufacturer (Precision Pharma, the production plant formerly owned by V.I. technologies) was no longer licensed to produce PLAS+SD and the Red Cross no longer held the license to distribute it.

11.2.1) HISTORICAL DEVELOPMENT

The American Red Cross (ARC) blood and derivatives organization comprises four areas within its "Biomedical Division":

1) Blood Services (cellular products)
2) Biomedical Division (plasma products)
3) Tissue Services, and
4) Research & Development (Jerome Holland Laboratory)

In 1985, the ARC signed a twenty-year agreement with Baxter allowing the ARC to use half of the plasma fractionation capacity of Baxter's (Hyland) fractionation plant in Glendale, California. The agreement included a R&D collaboration program allowing the ARC to use the Glendale facility for producing new plasma protein developed at the Jerome Holland Laboratory.

In 2000, approximately 0.8 million liters of recovered plasma were fractionated by Baxter in Glendale and 0.4 million liters by ZLB Bioplasma in Bern.

11.2.2) US SALES RESULTS

In 2001, the American Red Cross' sales of plasma-derived products (without PLAS+SD) was estimated as follows:

Product	*Dollars (MM)*	*Percent*
IGIV	236.6	62.4%
Fraction V	72.0	19.0%
Factor VIII	70.3	18.6%
Total	378.8	100.0%

The ARC's domestic sales history of plasma products is shown below:

American Red Cross Sales from 1987 to 2001
($Million)

	$MM	*Change*
1987	64.0	- 6%
1988	55.7	- 13%
1989	90.0	+ 62%
1990	108.0	+ 20%
1991	136.0	+ 26%
1992	145.0	+ 7%
1993	152.2	+ 5%
1994	104.1	- 32%
1995	144.3	+ 39%
1996	155.8	+ 8%
1997	156.8	+ 1%
1998	240.5	+ 53%
1999	288.5	+ 20%
2000	291.3	+ 1%
2001	378.8	+ 30%

The ARC products are produced from recovered plasma obtained from whole blood collected by the ARC Blood Services Regions. Each region supplies its hospitals with fresh frozen plasma, and the unused volume is "purchased" by National Headquarters for fractionation by Baxter or ZLB Bioplasma. The fee paid by the National Headquarters to its centers for the recovered plasma is not subjected to a commercial transaction or pricing. All the Red Cross plasma comes from voluntary, non-remunerated donors.

The new collection techniques, using either Haemonetics or Gambro blood+plasma collection machines have not received a strong acceptance as yet, partially attributed to the cost and partially to tradition. A few interviews with major blood centers indicated that less than 5% of the donations were made by means of such techniques in 2001. This may change rapidly as the donor pool does not increase fast enough in the coming years, and the manufacturers of these machines promote their products more aggressively to blood banks.

Plasma Units by Type of Use – 2001

Liters Fractionated	1,204,230
Liters used for Transfusion	400,126

Since 1997, the distribution of plasma products manufactured under the American Red Cross label is centralized in Louisville, Kentucky.

Marketing efforts have been undertaken in the last few years to increase the efficiency of the Red Cross Blood Services Regions in selling plasma derivatives in their respective area. The American Red Cross has 27 territory representatives and 3 district managers detailing hospital products (albumin and IVIG), as well as six sales representatives and six district managers dedicated to Monarc M's promotion.

11.2.3) PRODUCT LINE

Albumin and Plasma Protein Fraction (Fraction V)

"AlbumARC": Human Serum Albumin 5%. (250 ml & 500 ml) and "PlasmaARC": Human Serum Albumin 25%. (50 ml & 100 ml). The production of Plasma Protein Fraction 5% (250 ml & 500 ml) was discontinued in 1997.

Polyvalent Intravenous Immune Globulin (IGIV)

"Polygam SD" was introduced in 1987 in the U.S., and "Panglobulin", in 1998. Since the mid 1980's, the American Red Cross has been sending II+III paste derived from its plasma to ZLB Bioplasma for processing into "Sandoglobulin" which was distributed by Novartis. In 1997, the contract between the ARC and ZLB Bioplasma (then Swiss Red Cross ZLB) led to the creation of a new version of the IGIV made by ZLB. The product began to be commercialized under the brand name "Panglobulin" in mid-1998. The paste sent by the ARC to Bern represents 20% to 30% of the source material needed for making IGIV, the 70% to 80% remaining being manufactured as "Polygam SD".

Coagulation Factor Concentrates

"Monarc M" Monoclonal antibody-purified Factor VIII Concentrate, formerly called "Antihemophilic Factor, Method M."

Until recently, the ARC distributed "AlphaNine SD", a Factor IX concentrate made on contract by Alpha Therapeutic from ARC plasma. This agreement has been terminated. In early 2001, the ARC entered into an agreement for the distribution of Monarc-M by Alpha. This agreement has been terminated, too.

11.2.4) Research and Development

The Jerome H. Holland Laboratory for Biomedical Sciences, the ARC research laboratory facility located in Rockville, Maryland was opened in 1987. It comprises ten departments:

- Biochemistry Department
- Coagulation Proteins Department
- Experimental Pathology Department
- Immunology Department
- Molecular Biology Department
- Plasma Derivatives Department
- Platelet Biology Department
- Product Development Department
- Transmissible Disease Department, and
- Virology Department.

Research at the Holland Laboratory is supported by grants and contracts from the NIH, the CDC, private foundations and pharmaceutical firms. Its staff comprises over 200 research scientists. Some research and development activities are conducted by the Blood Services Regions as well.

In 1999, the American Red Cross signed an agreement with the Australian fractionator CSL Bioplasma to develop a fibrin sealant bandage comprising fibrinogen, thrombin and a resorbable supporting backing. Under the agreement, CSL Bioplasma will manufacture this

bandage-sealant for the American Red Cross. The product, which is in preclinical development, will be exclusively marketed by the Red Cross in the U.S. and by CSL Bioplasma in Australia, New Zealand and the Asian & Pacific region.

11.3) AVENTIS BEHRING

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King of Prussia, PA 19406-1310
Phone: (610) 878-4000
Fax: (610) 878-4040
Web: www.aventis.com

Aventis Behring has four plasma fractionation plants: one in Kankakee, Illinois, one (the former "Behringwerke") in Marburg, Germany, one in Vienna, one in Barcelona, Spain. The combined fractionation capacity of the four plants is about 3.6 million liters, the second largest after Baxter.

In early 2001, Aventis signed a non-binding letter of intent to sell a majority stake in Aventis Behring to Bayer Corporation. Details about the timing of financial aspects of the agreement were not disclosed. The joint venture combining Aventis Behring and Bayer's Biological Products unit would have sales in excess of $2 billion, and, according to an Aventis official, "would create an opportunity to expand product supply over time, with better utilization of plasma ... and a greater ability to invest in R & D, manufacturing capacity and more efficient manufacturing processes".

Bayer would bring to the joint venture its strength in the area of polyvalent IVIG and hyperimmune globulin preparations, alpha-1 antitrypsin and antithrombin III, as well as the technology and production facility of recombinant Factor VIII. For its part, Aventis Behring's special contribution to the joint venture would be Aventis Bio-Services' network of plasma collection centers, which would procure a substantial volume of plasma to the combined entity in the long run. Furthermore, Aventis Behring would bring its strength in human albumin, including recombinant albumin, and plasma-derived clotting factors.

Aventis Behring has 19 sales representatives and three regional managers detailing hemophilia products, as well as 35 representatives, five regional managers and four national accounts managers promoting

hospital products (immunology and critical care products, IVIG and albumin).

11.3.1) Historical Development

Armour established one of the country's first plasma fractionators after World War II. Its location in the middle west was decided for strategic reasons during the cold war. Over the following decades, Armour changed hands a number of times. Successive owners include Greyhound, Revlon, Pantry Pride, and, in the late 1990's, Rhône Poulenc/Rorer (RPR). In 1996, Armour and Behringwerke merged into a joint venture called "Centeon" which was renamed Aventis Behring when Aventis was created in December 1999 through the merger of the life sciences divisions of Hoechst and Rhône Poulenc.

Aventis Behring purchased a fractionation facility in Strasbourg, France and sold it to Octapharma in 1999. It also operated a small fractionation facility in Eschwege, Germany, closed in the 1980's.

11.3.2) US Sales Results

In 2001, the breakdown of Aventis Behring's sales by product including its recombinant Factor VIII ("Helixate") was:

Product	*Dollars (MM)*	*Percent*
IGIM	-	-
IGIV	155.3	39.6%
Fraction V	42.9	10.9%
Factor VIII	163.8	41.8%
Factor IX/PCC	30.1	7.7%
Total	392.1	100.0%

Without Bioclate and Helixate, the breakdown of Aventis Behring's sales was:

Product	*Dollars (MM)*	*Percent*
IGIM	-	-
IGIV	155.3	45.0%
Fraction V	42.9	12.4%
Factor VIII	117.1	33.9%
Factor IX/PCC	30.1	8.7%
Total	296.7	100.0%

Historical sales of Aventis Behring's plasma products in the U.S. is shown below:

Aventis Behring's Sales from 1987 to 2001
($Milllon)

	Without rFVIII		***With rFVIII***	
Year	*$Million*	*Change*	*$Million*	*Change*
1987	88.7	+ 1%		
1988	125.1	+ 41%		
1989	133.5	+ 7%		
1990	148.9	+ 12%		
1991	175.1	+ 18%		
1992	195.4	+ 12%		
1993	254.3	+ 30%		
1994	291.7	+ 15%		
1995	291.4	-	307.5	+ 22%
1996	242.2	- 17%	266.3	- 17%
1997	95.7	- 61%	140.4	- 47%
1998	117.3	+ 23%	210.3	- 33%
1999	212.9	+ 74%	293.3	- 32%
2000	291.1	+ 37%	378.7	+ 29%
2001	296.7	+ 16%	392.1	+ 2%

11.3.4) Product Line

Several products made by Aventis Behring's in Germany are not available on the US market, and may be introduced in the future.

Products licensed and/or commercialized in the United States

Coagulation Factor Concentrates

- "Helixate FS": recombinant Factor VIII. Helixate FS succeeds "Helixate", no longer available. It is made by Bayer and sold by Aventis Behring since 1994, following the settlement on patent issues between Bayer and Rhône Poulenc/Rorer.
- "Humate P": Factor VIII/von Willebrand complex. In 1986, Aventis Behring (then Armour) introduced "Humate P", the first product resulting from its relationship with Behring. Humate P was approved by the FDA for the treatment of vWD in June 1999.
- "Monoclate-P": monoclonal antibody-purified Factor VIII was introduced in the U.S. in 1987. In 1990, the pasteurized formulation of the product, renamed "Monoclate-P," was introduced to replace the heat-treated product.
- "Mononine" is called a "pure" Factor IX concentrate because it contains no measurable amounts of Factor II, VII, and X. It is monoclonal antibody-purified. It was introduced in mid-1992 in the U.S. and received an Orphan Drug Designation from the FDA.

Polyvalent Intravenous Immune Globulin (IGIV) and Hyperimmune Products

- "Gammar-P IV": polyvalent intravenous immune globulin. Initially approved in 1991 in the U.S., the pasteurized formulation was introduced in late 1995
- "Gammar": Intramuscular Polyvalent Immune Serum Globulin
- "Gamulin Rh": RhoD Immune Globulin
- "Plasma-Plex": Plasma Protein Fraction, - 5% (no longer manufactured)

Albumin and Plasma Protein Fraction (Fraction V)

- "Albuminar": Human Serum Albumin, - 5% and 25%

Products not commercialized in the United States (partial list: a number of hyperimmune globulin products are also available)

- "Beriate P": pasteurized Factor VIII
- "Berinin P": pasteurized high purity Factor IX
- "Beriplex P": Prothrombin Complex Concentrate (PCC)
- "Berinert P": C-1 inhibitor to treat hereditary angioedema
- "Kybernin P": Antithrombin III
- "Haemocomplettan P": human fibrinogen concentrate
- "Fibrogamin P": pasteurized Factor XIII
- "Gamma-venin P": polyvalent intravenous immune globulin, and
- "Venimun": polyvalent intravenous immune globulin, and

11.3.5) Research and Development

- Clinical trial of "Beriglobin P" for the treatment of primary immune deficiency by subcutaneous injection. The trial is reported to involve some sixty patients.

- Aventis Behring is collaborating with "Inhale Therapeutic Systems" (Palo Alto, CA) on a new formulation of alpha-1 proteinase inhibitor for the treatment of patients with alpha-1 antitrypsin deficiency. Under the agreement, Aventis Behring will manufacture the alpha-1 proteinase inhibitor from plasma at a new facility, manage the clinical trials and commercialize the lyophilized formulation prepared by Inhale. Aventis Behring will have marketing rights worldwide except in Japan (where the disease has a low prevalence anyway) while Inhale will receive royalties on product sales, an up-front fee, R & D funding and various milestone payments. In addition to supplying the product in a powder-form, Inhale will supply its proprietary delivery device to Aventis Behring for commercialization. The product developed by Inhale Therapeutic has received Orphan Drug status in Europe, and clinical trials have begun in the United States

- In December 2001, Aventis Behring signed an agreement with the Australian firm "Gradipore" for the separation of and purification of immune globulins from plasma fractions, using the latter's platform separation technology consisting in a unique membrane-based biological separation system.

- Development of a recombinant albumin in yeast by "Delta Biotechnology" (Nottingham, UK). The product, named "Recombumin" was used by Merck as an excipient in its investigational measles, mumps and rubella (MMR) vaccine in 2001. Recombumin was tested in 2000 in double blind, Phase I clinical trials with 530 subjects, and was shown to be generally well tolerated.

11.4) BAXTER BIOSCIENCE

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Phone (818) 956-3200
Web: www.baxterbioscience.com

In 2001, Baxter was again the market leader with $466.6 million in sales and held a 22.9% market share. Baxter's sales amounted to $905.8 million with recombinant (31.1% market share). Sales grew by 23.8% without rFVIII, and by 27.0% with rFVIII.

With four fractionation plants in Glendale, California, Rochester, Michigan, Vienna, Austria and Rieti, Italy, Baxter is the world's largest fractionator with a combined capacity of more than four million liters of plasma per year. It also owns and operates over 110 plasma collections centers and plans to open more in the coming years. In early, the company announced that 22 new centers would be opened in the next two years.

As far as the therapeutic proteins are concerned, the company is organized in four main sectors:

- Recombinant Proteins involving "Recombinate" and the new albumin-free recombinant Factor VIII under development,
- Plasma Proteins involving the plasma-derived Factor VIII and IX concentrates ("Hemofil-M", "Feiba VH", "Proplex T", "Bebulin VH", and albumin in U.S.), and several other products sold outside the U.S. ("Immunate", "Immunine", "Prothromplex T, to name but a few),
- Wound Management involving the fibrin sealant "Tisseel" (sold as "Tissucol" and some countries, and related products,
- Antibody Therapy involving "Gammagard SD", "Iveegam" and other polyvalent and hyperimmune globulin Preparations, most of which are manufactured in Vienna.

In 1998, the FDA approved a new manufacturing facility in Thousand Oaks, California for the production of "Recombinate". This plant was reported to enable Baxter to increase its production by about 40% initially, and more after further expansion steps.

Baxter is building a new plasma fractionation facility adjacent to its existing plant in Glendale, California in order to increase the production of Gammagard SD, among others. The new fractionation site is expected to be operational in 2003.

In early 2002, Baxter acquired Fusion Medical Technologies for about $157 million. Fusion's "FloSeal" collagen-based fibrin sealant provides Baxter BioScience with "an array of solutions to seal tissue, enhance wound healing and manage hemostasis".

"Arriva" has a joint research collaboration with Baxter Bioscience to develop a recombinant Alpha One Antitrypsin in yeast for the treatment of hereditary emphysema, asthma and other respiratory disorders.

In 2001, Baxter Bioscience has 20 sales representatives detailing hospital products. Tisseel is promoted by a dedicated sales force.

11.4.1) U.S. SALES RESULTS

In 2001, Baxter's sales by product in the United States were recorded as follows:

With Recombinant Factor VIII

Product	*Dollars (MM)*	*Percent*
IGIV	242.3	26.7%
Fraction V	59.9	6.6%
Factor VIII	519.2	57.3%
Factor IX/PCC		
0.8	0.1%	
aPCC	52.3	5.8%
Fibrin Glue	31.3	3.5%
Total	905.8	100.0%

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Without Recombinant Factor VIII

Product	*Dollars (MM)*	*Percent*
IGIV	242.3	51.9%
Fraction V	59.9	12.8%
Factor VIII	80.0	17.2%
Factor IX/PCC	0.8	0.2%
aPCC	52.3	11.2%
Fibrin Glue	31.3	6.7%
Total	466.6	100.0%

Baxter's domestic sales history is shown below:

Baxter Biosciences' Sales from 1987 to 2001
($Million)

	Without rFVIII		***With rFVIII***	
Year	*$MM*	*Change*	*$MM*	*Change*
1987	70.2	+ 5%		
1989	122.0	+ 24%		
1991	129.1	+ 6%		
1993	153.2	+ 5%		
1995	159.2	+ 14%	271.0	+ 19%
1996	172.6	+ 8%	311.9	+ 15%
1997	172.8	-	316.8	+ 2%
1998	273.5	+ 58%	446.3	+ 41%
1999	296.0	+ 10%	600.5	+ 32%
2000	376.8	+ 27%	713.4	+ 19%
2001	466.6	+ 24%	905.8	+ 27%

Several products made by Baxter in Austria are not available on the U.S. market, and may be introduced in the future.

11.4.2) PRODUCT LINE

Products licensed and/or commercialized in the United States

Coagulation Factor Concentrates

- "Recombinate": recombinant Factor VIII introduced in December 1992 in the U.S. In mid 2002, Baxter filed a Biologic License application for a second generation recombinant Factor VIII product which does not contain any human albumin in either the final container or the cell growth medium.
- "Hemofil M", a monoclonal antibody-purified plasma-derived Factor VIII concentrate. The product in its present formulation was approved by the FDA in 1988. Its predecessor, "Hemofil HT" was approved by the FDA in 1983
- "Proplex T", a Factor IX Complex concentrate, or PCC, used for the treatment of Factor VII-deficient patients, some inhibitor to Factor VIII patients, and a few Factor IX-deficient patients.
- "Feiba VH", an activated Factor Complex concentrate, introduced in the early 1980's

Polyvalent Intravenous Immune Globulin (IGIV) and Hyperimmune Products

- "Gammagard S/D" is a polyvalent intravenous immune globulin (IVIG) approved in 1986 in the U.S. The product is manufactured partially in Glendale, California and in Lessines, Belgium. Gammagard was approved for the treatment of B-cell chronic lymphocytic leukemia (CLL) in 1989. It has a lower IgA content than the other IGIV preparations on the market.
- "Iveegam" a polyvalent intravenous immune globulin manufactured in Vienna, Austria.

Albumin and Plasma Protein Fraction (Fraction V)

"Buminate-5%": Human Serum Albumin 5%.

"Buminate-25%": Human Serum Albumin 25%

Baxter is no longer producing "Protenate", a Plasma Protein Fraction 5%.

Fibrin Sealants

"Tisseel": Fibrin Sealant comprising human thrombin, fibrinogen and aprotinin was approved in 1999 in the United States.

Products not commercialized in the United States (partial list: a number of hyperimmune globulin products are also available)

- "Immunate", a Factor VIII concentrate
- "Immunine", a Factor IX concentrate
- "Antithrombin III"
- "C1-Inhibitor"
- "Ceprotin (Protein C)"
- "Fibrinogen"

11.4.3) RESEARCH AND DEVELOPMENT

Over the years, Baxter has formed various alliances through licensing, partnerships, and joint ventures. Among others:

- Partnership with Cerus for the development of a pathogen inactivation technology of several blood products using "Intercept", a Ultra Violet light-activated "psoralens technology" to inactivate viruses and other blood-borne infectious agents.

- In 1999, Alliance Pharmaceutical and Baxter signed an agreement providing Baxter with exclusive rights to manufacture, sell and distribute Alliance's "Oxygent" perfluorochemical emulsion in the U.S. Canada and Europe. An international Phase III study involving 492 general surgery patients "demonstrated that Oxygent treatment provided a statistically significant reduction of blood usage".

- Researcher at Baxter in Austria developed a process for the purification of Alpha. One Proteinase inhibitor. It is derived from fractions IV 1-4 using ethanol precipitation and Q-Sepharose chromatography.

- A subsidiary of Baxter purchased the assets and exclusive worldwide rights to the technology for "a unique and proprietary" recombinant erythropoietin for the treatment of anemia.

- Baxter submitted a 510(k) application seeking FDA clearance for its new "ALYX" automated blood collection system to collect two units of leukoreduced red blood cells from a single donor. Additional protocols for separation and collection of selective blood components are under development. The ALYX system includes a filter to leukoreduce all the red cells prior to separation into two blood bags.

11.5) BAYER CORPORATION

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Research Triangle Park, NC 27709
Phone: (919) 277-2720
Web: www.bayer.com

In 2001, Bayer (Biological Products Unit) sales amounted to $336.6 million, a -10.5% decline from the previous year. This decline was attributed to lower sales of most products, in particular some hyperimmune globulin products, albumin, Alpha One Antitrypsin, and Antithrombin III. When including recombinant Factor VIII, sales amounted to $370.8 million (-17.6%), a result caused by the disappointing performance of Kogenate FS.

Bayer operates two plasma fractionation plants. The largest one, in Clayton, North Carolina has a capacity of two million liters per year. The company's first plant in Berkeley, California, is used for producing the initial steps of Alpha One Antitrypsin and Antithrombin III. In recent years, the Clayton facility was upgraded and expanded to produce more IGIV and Alpha-1 Antitrypsin.

In 2000, Bayer received FDA approval for "Kogenate SF" (Sucrose Formulated), a second-generation recombinant Factor VIII stabilized in final container without human albumin. The first formulation of "Kogenate" was immediately phased out upon the introduction of the new product. Through 2001, the production of Kogenate FS and Helixate FS suffered numerous production difficulties, which led to a shortage of products. In 2002, the production gradually resumed, and is expected to reach a normal level by early 2003.

In early 2001, Aventis signed a non-binding letter of intent to sell a majority stake in Aventis Behring to Bayer Corporation (see above under para 11.3).

Bayer's sales force for biological products includes 40 sales representatives and five "Division Sales Managers.

11.5.1) COMPANY HISTORY

Bayer is the US subsidiary of Bayer AG, Leverkusen, Germany. In the 1980's Bayer AG (Leverkusen) bought Miles Laboratories and made it its U.S. pharmaceutical subsidiary. In the 1960's, Bayer AG also acquired Cutter Laboratories and kept the name until the mid-1980's. In the late 1970's, Bayer began to consolidate its U.S. pharmaceutical operations, and in 1983, Cutter became an operational division of Miles Laboratories.

In 1999, Bayer's biological operations were relocated to Research Triangle Park, North Carolina, near its plasma fractionation plant in Clayton. In 2001, this division became completely independent from the pharmaceutical division.

11.5.2) U.S. SALES RESULTS

In 2001, Bayer's sales by product, including Kogenate were:

With Recombinant Factor VIII

Product	*Dollars (MM)*	*Percent*
IGIM	37.2	10.0%
IGIV	190.4	51.3%
Fraction V	12.6	3.4%
Factor VIII	38.8	10.6%
Antithrombin III	2.7	0.7%
Alpha One Antitrypsin	89.2	24.0%
Total	370.8	100.0%

Without Recombinant Factor VIII

Product	*Dollars (MM)*	*Percent*
IGIM	37.2	11.1%
IGIV	190.4	56.5%
Fraction V	12.6	3.7%
Factor VIII	4.6	1.4%
Antithrombin III	2.7	0.8%
Alpha One Antitrypsin	89.2	26.5%
Total	336.6	100.0%

Bayer's last twelve year domestic US plasma fraction sales history is:

Bayer Corporation (Biological) Sales from 1987 to 2001 ($Million)

	Without rFVIII		***With rFVIII***	
Year	*$Million*	*Change*	*$Million*	*Change*
1987	86.5	+16%		
1989	154.3	+25%		
1991	179.2	+ 4%		
1993	220.9	+13%		
1995	221.9	-11%	266.8	- 12%
1996	249.5	+ 2%	307.6	+ 15%
1997	295.2	+18%	362.4	+ 18%
1998	272.7	- 7%	382.3	+ 6%
1999	357.6	+ 31%	433.2	+ 13%
2000	376.0	+ 5%	449.8	+ 4%
2001	336.6	- 11%	370.8	- 18%

11.5.3) PRODUCT LINE

Bayer offers the broadest range of plasma products among all the U.S. fractionators. Bayer's portfolio in the US market includes:

Polyvalent Intravenous Immune Globulin (IGIV) and Hyperimmune Products

- "Gamimune N": Polyvalent Intravenous Gamma Globulin (IGIV, 10% and 5% solutions). Bayer has developed a new liquid IVIG called "Gamunex". Its manufacturing process uses a new technology resulting in a "purer" product than Gamimune-N and generating higher yields. Bayer will produce Gamunex in a new facility solely dedicated to this product. The product may be launched in 2003, as a BLA has already been filed.
- "BayGam" Polyvalent Intramuscular Immune Globulin. 2mL.
- "BayTet", Tetanus Immune Globulin.
- "BayHep B", Hepatitis B Immune Globulin.
- "BayRab", Rabies Immune Globulin.
- "BayRho(D)", Rho(D) Immune Globulin.

Albumin and Plasma Protein Fraction (Fraction V)

- "Plasbumin-5": Human Serum Albumin 5%
- "Plasbumin-25": Human Serum Albumin 25%
- "Plasmanate": Plasma Protein Fraction

Coagulation Factor Concentrates

- "Kogenate FS": Coagulation Factor VIII (recombinant, sucrose-formulated)
- "Koate DVI": Coagulation Factor VIII (plasma-derived), approved in 1999, and replacing "Koate HP" launched ten years earlier.

Bayer does not produce any Factor IX concentrate (the production of a Factor IX Complex concentrate "Konyne 80" ended some tow years ago) but signed an agreement with Avigen, a California-based which developed a product called "Goagulin B" which enables the production of Factor IX in hemophilia B patients. The procedure is in phase II clinical trial.

Others Products

- "Prolastin": alpha-1 antitrypsin, launched in 1987.
- "Thrombate III": antithrombin III, approved in 1991. The product is heat-treated and sold in 500 or 1,000 IUs vials.

11.6) BIOPORT CORPORATION

3500 N. M. Luther King Jr. Blvd.
Lansing, MI 48906
Web: www.bioport.com

In 1996/97, the Michigan Biologic Products Institute was privatized. Bioport, a joint venture firm, acquired it at the end of 1997.

In 1999, Bioport reported a fractionation capacity of 85,000 liters per year. The plasma processed was mostly collected in the state of Michigan. From 1999 onwards, the FDA uncovered a number of GMPs deviations in the production, due to the age of this fractionation plant. Bioport decided to close it indefinitely in 2001. Bioport now produces only vaccines in particular the Anthrax vaccine for the U.S. armed forces.

11.7) MASSACHUSETTS BIOLOGIC LABORATORY

305 South Street
Jamaica Plains, MA 02130
Phone: (617) 983-6400
Fax: (617) 983-9081

The Massachusetts Biologic Laboratory has a capacity of 250,000 liters of plasma per year. Most of its recovered plasma is provided by the American Red Cross, Northeastern region, while Nabi supplies another 100,000 liters of hyperimmune plasma. This institute produces:

- Polyvalent intramuscular immune globulin,
- Human albumin,
- Respiratory Syncytial Virus immune globulin ("RespiGam") on contract with MedImmune
- Cytomegalovirus immune globulin ("CytoGam") on contract with MedImmune,
- Varicella-Zoster immune globulin.

Since 1996, all the immune globulin products made by this Laboratory are solvent detergent-treated. Since 1959, the Massachusetts Biologic Laboratory has contracted with the State of Massachusetts Department of Public Health for the development of vaccines and other products. At the beginning of 1997, the control of the Laboratory was transferred to the University of Massachusetts.

11.8) NOVARTIS PHARMACEUTICALS

59 Route 10
East Hanover, NJ 07936-1080
Phone: (973) 781-7109
Web: www.novartis.com

Novartis Pharmaceuticals is the U.S. subsidiary of the Swiss pharmaceutical firm based in Basel, Switzerland. The company has distributed "Sandoglobulin" made by the ZLB of the Swiss Red Cross since the product introduction in the early 1980's. As the ZLB was acquired by the Australian fractionator CSL Bioplasma in September 2000, Novartis lost its distribution franchise in the U.S. at the end of 2000. In 2001, the company sold its inventory until it was entirely depleted. Novartis is no longer in the plasma business.

11.9) PRECISION PHARMACEUTICALS

155 Duryea Road
Melville, NY 11747
Phone: (631) 845-6110
Fax: (631) 752-7354
Web: www.precisionpharma.com

11.9.1) HISTORICAL DEVELOPMENT

In the late 1970's, the New York Blood Center built a fractionation plant in Melville, New York (on Long Island). It was licensed by the FDA in 1980 and began fractionating plasma collected in the New York area. In 1995, the New York Blood Center spun off its fractionation plant which was acquired by "Ampersand Ventures", a venture capital organization of Wellesley, Massachusetts, which renamed it "Melville Biologics". In 1998, it was renamed "V.I. Technologies", or "Vitex", and

began to produce virus inactivated frozen plasma ("PLAS+SD") under an agreement with the American Red Cross, using its proprietary solvent detergent virus inactivation method.

At the end of 1999, Vitex and Pentose Pharmaceuticals merged. The latter developed a virus inactivation for red cells, called "Inactine". In mid-2001, Vitex spinned off its fractionation facility and SD Plasma manufacturing operations, and a management buy-out led to the creation of "Precision Pharmaceuticals" which only fractionates plasma on contract with Bayer.

Several years ago, Bayer entered into an agreement with the company for custom fractionation in exchange for a substantial investment to renovate and upgrade of the fractionation facility.

11.10) WYETH

555 East Lancaster Avenue
St Davids, PA 19087
Phone: (610) 964-4400
Web: www.wyeth.com

In March 2000, ReFacto received FDA approval in the United States. It is a "third-generation" recombinant Factor VIII, in which the B-domain of the Factor VIII molecule has been deleted. It is formulated without human albumin as a stabilizer, which characterize the "second generation" concentrates but the medium contains albumin. The product was launched in early 2001 in the U.S.

Wyeth/Genetics Institute produces and sells "BeneFIX" in the United States.16 sales representatives and two regional managers are dedicated to these products.

11.11) ZLB BIOPLASMA

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Suite 1150
Glendale, CA 91203
Phone: (818) 244-2952
Fax: (818) 244-9952
Web: www.zlbusa.com

Following the acquisition of the Central Laboratory of the Swiss Red Cross (ZLB) by the Australian firm CSL Limited, ZLB Bioplasma, Inc. was created in Glendale, California and took over the commercial functions of Novartis and Alpine Biologics. ZLB Bioplasma sells IVIG and some albumin. Its sales force comprises approximately 20 representatives. In 2001 and 2002, ZLB Bioplasma secured several major supply contracts with group purchase organizations s, including Novations and McKesson.

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